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(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: The invention provides a compound of formula (I): wherein R^1, R^2, R^3, R^4, R^5, N, X and Y are as defined in the specification, processes, for their preparation, pharmaceutical compositions containing them, and their use in therapy, especially for the treatment of chemokine receptor related diseases and conditions.

CHEMICAL COMPOUNDS

The present invention relates to substituted piperidine compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

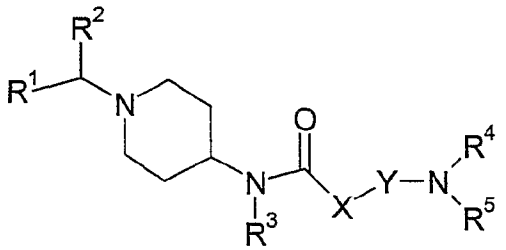
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

The present invention provides a compound of formula (I):



(I)

wherein:

R^1 is phenyl which is optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, nitro or cyano;

R^2, R^3 and R^4 are, independently, hydrogen or C_{1-4} alkyl;

R^5 is C_{1-6} alkyl, aryl, heteroaryl, aryl(C_{1-4})alkyl, heteroaryl(C_{1-4})alkyl or C_{3-8} cycloalkyl; wherein the aryl and heteroaryl moieties of R^5 are optionally substituted by halogen, C_{1-6} alkyl (optionally substituted by halogen, C_{1-6} alkoxy or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)), OR^6, $S(O)_mR^7$, $S(O)_2NR^8R^9$, $NR^{10}S(O)_2R^{11}$, $C(O)R^{12}$, $C(O)NR^{13}R^{14}$, $NR^{15}C(O)R^{16}$, $NR^{17}R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, methylenedioxy, nitro or cyano;

X is $(CH_2)_n$, where n is 1, 2, 3 or 4;

Y is a 2,4-, 2,5- or 3,5- linking 5-membered heteroaryl ring comprising 2 or 3 heteroatoms independently selected from the group comprising nitrogen, oxygen and sulphur, wherein Y is optionally substituted by C_{1-4} alkyl;

R^6, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are, independently, hydrogen or C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no acetal or aminal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3));

R^7 and R^{11} are, independently, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no thioacetal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3));

R^{12} is hydrogen, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no acetal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)) or C_{1-6} alkoxy (unsubstituted or mono-substituted by C_{1-6} alkoxy or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3));

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof.

Compounds of formula (I) are capable of existing in isomeric forms (for example as tautomers, enantiomers, geometric isomers or diastereomers). The present invention encompasses all such isomers and mixtures thereof in all proportions.

The group Y is a 2,4- or 2,5-linked imidazolyl ring, oxazolyl or thiazolyl ring, a 2,5-linked 1,3,4-oxadiazolyl or 1,3,4-thiadiazolyl ring, or a 3,5-linked isoxazolyl, isothiazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl or 1,2,4-thiadiazolyl ring.

Aryl is, for example, phenyl or naphthyl. In one aspect of the invention aryl is phenyl.

Heteroaryl is an aromatic, mono- or bi-cyclic ring system preferably comprising 1, 2 or 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur. Heteroaryl is, for example, imidazolyl, thienyl, furyl, pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, 1,2,3-, 1,2,4- or 1,3,5-triazinyl, benzo[b]thienyl, benzo[b]furyl, indolyl or quinolinyl. In another aspect of the invention heteroaryl is monocyclic.

Alkyl groups are straight or branched chain and are, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl or tert-butyl. Alkoxy groups are straight or branched chain and are, for example, methoxy, ethoxy, n-propoxy, iso-propoxy or tert-butoxy. Haloalkyl is preferably alkyl optionally substituted with 1, 2 or 3 chloro or fluoro atoms, and is, for example, CF_3.

Cycloalkyl is mono- or bi-cyclic and is, for example, cyclopropyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl or bicyclo[2.2.2]octyl.

Arylalkyl is, for example, benzyl, 2-phenyleth-1-yl or 1-phenyleth-1-yl. Heteroarylalkyl is, for example, pyridinylmethyl, pyrimidinylmethyl or furylmethyl.

A suitable salt of a compound of formula (I) includes a chloride, bromide, tosylate, mesylate, sulphate or phosphate salt.

In one particular aspect the invention provides a compound of formula (I) wherein: R^1 is phenyl which is optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, nitro or cyano; R^2, R^3 and R^4 are, independently, hydrogen or C_{1-4} alkyl; R^5 is aryl, heteroaryl, aryl(C_{1-4})alkyl or heteroaryl(C_{1-4})alkyl; wherein the aryl and heteroaryl moieties of R^5 are optionally substituted by halogen, C_{1-6} alkyl (optionally substituted by halogen, C_{1-6} alkoxy or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)), OR^6, $S(O)_mR^7$, $S(O)_2NR^8R^9$, $NR^{10}S(O)_2R^{11}$, $C(O)R^{12}$, $C(O)NR^{13}R^{14}$, $NR^{15}C(O)R^{16}$, $NR^{17}R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, methylenedioxy, nitro or cyano; X is $(CH_2)_n$, where n is 1, 2, 3 or 4; Y is a 2,4-, 2,5- or 3,5- linking 5-membered heteroaryl ring comprising 2 or 3 heteroatoms independently selected from the group comprising nitrogen, oxygen and sulphur, wherein Y is optionally substituted by C_{1-4} alkyl; R^6, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are, independently, hydrogen or C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no acetal or aminal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)); R^7 and R^{11} are,

independently, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no thioacetal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)); R^{12} is hydrogen, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no acetal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)) or C_{1-6} alkoxy (unsubstituted or mono-substituted by C_{1-6} alkoxy or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)); or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof.

In a further aspect of the invention n is 2.

In a still further aspect of the invention R^1 is phenyl optionally substituted by C_{1-4} alkyl (such as methyl), C_{1-4} alkoxy (such as methoxy) or halogen (such as chloro or fluoro). The group R^1 can be phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-fluoro-4-chlorophenyl, 3-fluoro-4-methoxyphenyl or 2-methyl-3-fluorophenyl. The group R^1 is, for example, 3,4-dichlorophenyl or 3,4-difluorophenyl.

In yet another aspect of the invention R^2 is hydrogen.

In a further aspect of the invention R^3 is hydrogen.

In a still further aspect of the invention R^4 is hydrogen.

In another aspect of the invention R^5 is C_{1-6} alkyl (such as methyl or propyl), C_{3-8} cycloalkyl (such as cyclopropyl, cyclohexyl or bicyclo[2.2.1]heptyl), phenyl, monocyclic heteroaryl, benzyl or monocyclic heteroarylmethyl, wherein the phenyl and heteroaryl moieties of R^5 are optionally substituted by halogen (such as chloro or fluoro), C_{1-4} alkyl (such as methyl and iso-propyl), C_{1-4} alkoxy (such as methoxy), C_{1-4} haloalkyl (such as CF_3), methylenedioxy, $C(O)(C_{1-4}$ alkyl) (such as acetyl), C_{1-4} thioalkyl (such as SCH_3), cyano, $N(C_{1-4}$ alkyl$)_2$ (such as $N(CH_3)_2$), $NHC(O)(C_{1-4}$ alkyl) (such as $NHC(O)CH_3$), $C(O)N(C_{1-4}$ alkyl$)_2$ (such as $C(O)N(CH_3)_2$) or $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$).

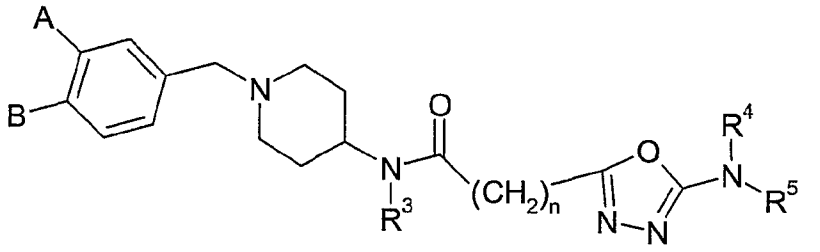
In yet another aspect of the invention R^5 is phenyl, monocyclic heteroaryl, benzyl or monocyclic heteroarylmethyl, wherein the phenyl and heteroaryl moieties of R^5 are optionally substituted by halogen (such as chloro or fluoro), C_{1-4} alkyl (such as methyl and iso-propyl), C_{1-4} alkoxy (such as methoxy), C_{1-4} haloalkyl (such as CF_3), methylenedioxy, $C(O)(C_{1-4}$ alkyl) (such as acetyl), C_{1-4} thioalkyl (such as SCH_3), cyano, $N(C_{1-4}$ alkyl$)_2$ (such as $N(CH_3)_2$), $NHC(O)(C_{1-4}$ alkyl) (such as $NHC(O)CH_3$), $C(O)N(C_{1-4}$ alkyl$)_2$ (such as $C(O)N(CH_3)_2$) or $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$).

Monocyclic heteroaryl is, for example, pyridinyl, furyl or thiazolyl.

In a further aspect R^5 is 2,4-difluorophenyl, 2-pyridyl, 3-pyridyl, 2- fluorophenyl, 2- chlorophenyl or 3-cyanophenyl.

In a still further aspect Y is a 2,5-linked thiazolyl ring (optionally substituted with C_{1-4} alkyl, for example methyl), or a 3,5-linked 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl or 1,3,4-thiadiazolyl ring. For example, Y is 3,5-linked 1,2,4-oxadiazolyl or 2,5-linked thiazolyl.

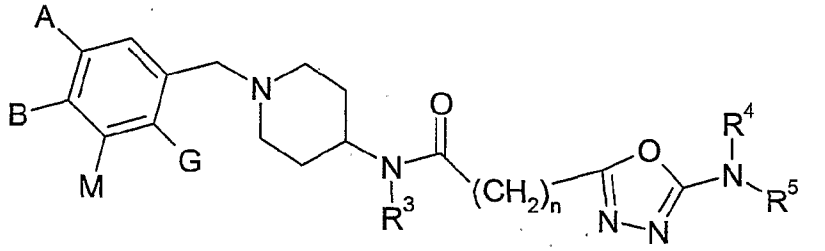
In another aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein A and B are (for example, independently) chloro or fluoro, and R^3, n, R^4 and R^5 are as defined above.

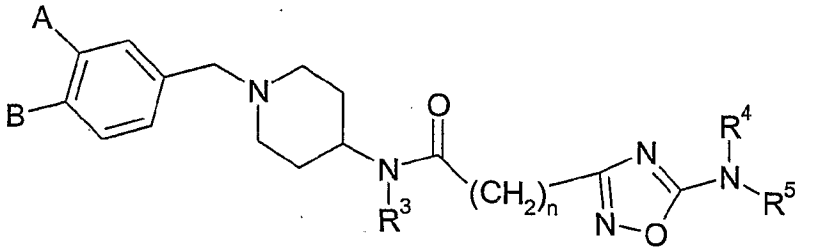
In yet another aspect the present invention provides a compound of formula (Ia'):



(Ia')

wherein A, B, G and M are, independently, hydrogen, chloro, fluoro, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy), and R^3, n, R^4 and R^5 are as defined above.

In another aspect the present invention provides a compound of formula (Ib):

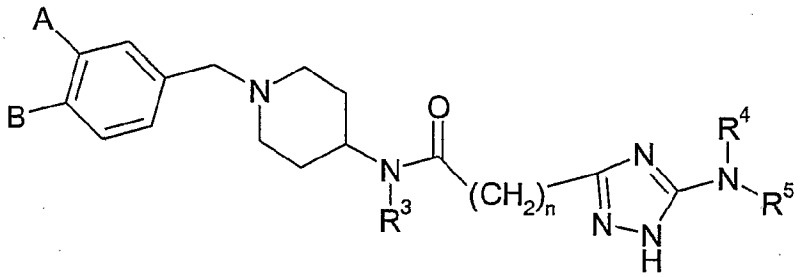


(Ib)

wherein A and B are (for example, independently) chloro or fluoro, and R^3, n, R^4 and R^5 are as defined above.

In yet another aspect the present invention provides a compound of formula (Ib'), wherein A, B, G and M are, independently, hydrogen, chloro, fluoro, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy), and R^3, n, R^4 and R^5 are as defined above.

In another aspect the present invention provides a compound of formula (Ic):

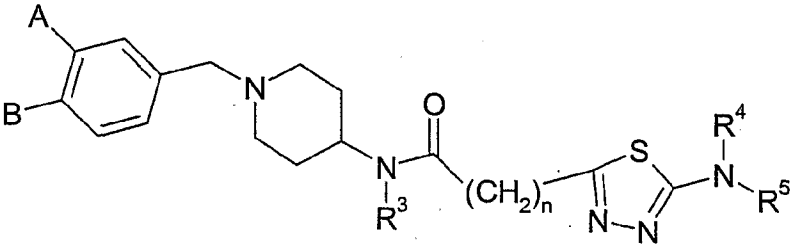


(Ic)

wherein A and B are (for example, independently) chloro or fluoro, and R^3, n, R^4 and R^5 are as defined above.

In yet another aspect the present invention provides a compound of formula (Ic'), wherein A, B, G and M are, independently, hydrogen, chloro, fluoro, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy), and R^3, n, R^4 and R^5 are as defined above.

In another aspect the present invention provides a compound of formula (Id):

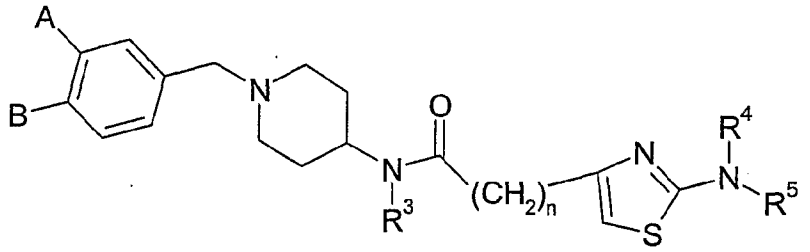


(Id)

wherein A and B are (for example, independently) chloro or fluoro, and R^3, n, R^4 and R^5 are as defined above.

In yet another aspect the present invention provides a compound of formula (Id'), wherein A, B, G and M are, independently, hydrogen, chloro, fluoro, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy), and R^3, n, R^4 and R^5 are as defined above.

In another aspect the present invention provides a compound of formula (Ie):

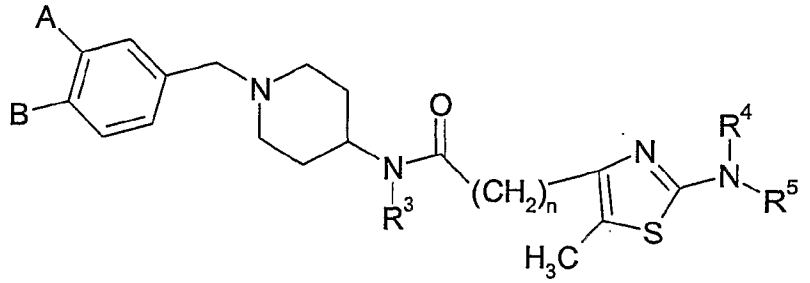


(Ie)

wherein A and B are (for example, independently) chloro or fluoro, and R^3, n, R^4 and R^5 are as defined above.

In yet another aspect the present invention provides a compound of formula (Ie'), wherein A, B, G and M are, independently, hydrogen, chloro, fluoro, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy), and R^3, n, R^4 and R^5 are as defined above.

In another aspect the present invention provides a compound of formula (If):



(If)

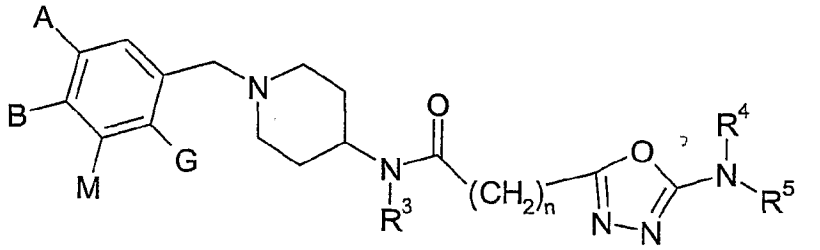
wherein A and B are (for example, independently) chloro or fluoro, and R^3, n, R^4 and R^5 are as defined above.

In yet another aspect the present invention provides a compound of formula (If'), wherein A, B, G and M are, independently, hydrogen, chloro, fluoro, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy), and R^3, n, R^4 and R^5 are as defined above.

Examples of compounds of the invention are presented in the Tables below.

TABLE I

All compounds in Table I are of formula (Ia'):



(Ia')

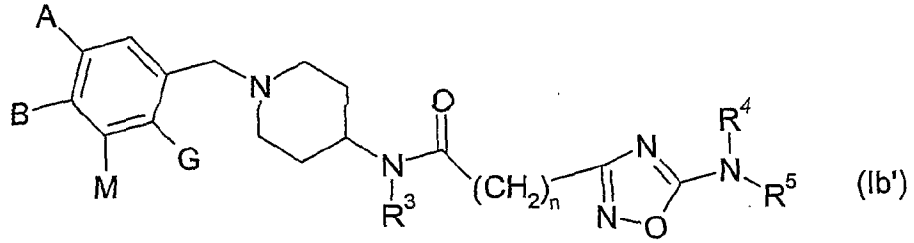
Compound No.	A	B	G	M	n	R^3	R^4	R^5
1	Cl	Cl	H	H	1	H	H	C_6H_5
2	Cl	Cl	H	H	1	H	H	4-OCH_3-C_6H_4
3	Cl	Cl	H	H	1	H	H	2-CH_3-C_6H_4
4	Cl	Cl	H	H	1	H	H	Pyridin-3-yl
5	Cl	Cl	H	H	1	H	H	2-Cl-C_6H_4
6	Cl	Cl	H	H	2	H	H	2-Cl-C_6H_4
7	Cl	Cl	H	H	2	H	H	4-OCH_3-C_6H_4
8	Cl	Cl	H	H	2	H	H	2-OCH_3-C_6H_4
9	Cl	Cl	H	H	2	H	H	3,4-Methylenedioxyphenyl
10	Cl	Cl	H	H	2	H	H	4-CH_3-C_6H_4
11	Cl	Cl	H	H	2	H	H	Pyridin-3-yl
12	Cl	Cl	H	H	2	H	H	3-Cl-C_6H_4
13	F	F	H	H	2	H	H	3-C(O)CH_3-C_6H_4
14	F	F	H	H	2	H	H	4-CN-C_6H_4
15	F	F	H	H	2	H	H	2,4-F_2-C_6H_3
16	F	F	H	H	2	H	H	2-OCH_3-C_6H_4
17	F	F	H	H	2	H	H	2,6-F_2-C_6H_3
18	F	F	H	H	2	H	H	3-SCH_3-C_6H_4
19	F	F	H	H	2	H	H	3-CN-C_6H_4
20	F	F	H	H	2	H	H	4-CH_3-C_6H_4
21	F	F	H	H	2	H	H	4-Cl-C_6H_4
22	F	F	H	H	2	H	H	2-Cl-C_6H_4
23	F	F	H	H	2	H	H	2-F-C_6H_4
24	F	F	H	H	2	H	H	2-CH_3-C_6H_4
25	F	F	H	H	2	H	H	4-N(CH_2CH_3)$_2$-C_6H_4
26	F	F	H	H	2	H	H	Pyridin-3-yl
27	F	F	H	H	2	H	H	3-Cl-C_6H_4
28	F	F	H	H	2	H	H	2,4-Cl_2-C_6H_3
29	F	F	H	H	2	H	H	4-N(CH_3)$_2$-C_6H_4

30	F	F	H	H	2	H	H	4-SCH_3-C_6H_4
31	F	F	H	H	2	H	H	3,4-Methylenedioxyphenyl
32	F	F	H	H	2	H	H	4-$S(O)_2NH_2$-C_6H_4
33	F	F	H	H	2	H	H	4-$NHC(O)CH_3$-C_6H_4
34	F	F	H	H	2	H	H	3-$NHC(O)CH_3$-C_6H_4
35	F	F	H	H	2	H	H	3-$C(O)N(CH_3)_2$-C_6H_4
36	F	F	H	H	2	H	H	4-$C(O)N(CH_3)_2$-C_6H_4
37	F	F	H	H	2	H	H	Pyridin-2-yl
38	F	F	H	H	2	H	H	4-$S(O)_2CH_3$-C_6H_4
39	F	F	H	H	2	H	H	3-$S(O)_2CH_3$-C_6H_4
40	F	F	H	H	2	H	H	2,5-F_2-C_6H_3
41	F	F	H	H	2	H	H	2-$CH(CH_3)_2$-C_6H_4
42	F	F	H	H	2	H	H	2-CF_3-C_6H_4
43	F	F	H	H	2	H	H	2,4,5-F_3-C_6H_2
44	F	F	H	H	2	H	H	2-Cl-5-CF_3-C_6H_3
45	F	F	H	H	2	H	H	3-F-C_6H_4
46	F	F	H	H	2	H	H	C_6H_5
47	F	F	H	H	2	H	H	2-CH_3-4-F-C_6H_3
48	F	F	H	H	2	H	H	Thiazol-2-yl
49	F	F	H	H	2	H	CH_3	2,4-F_2-C_6H_3
50	Cl	Cl	H	H	2	H	CH_3	Pyridin-3-yl
51	Cl	Cl	H	H	2	CH_3	H	Pyridin-3-yl
52	F	F	H	H	2	H	H	CH_2(pyridin-3-yl)
53	F	F	H	H	2	H	H	CH_2(2-F-C_6H_4)
54	F	F	H	H	2	H	H	CH_2(4-OCH_3-C_6H_4)
55	F	F	H	H	2	H	H	CH_2(fur-2-yl)
56	F	F	H	H	2	H	H	Cyclohexyl
57	F	F	H	H	2	H	H	2,6-$(CH_3)_2$-C_6H_3
58	F	F	H	H	2	H	H	Bicyclo[2.2.1]hept-2-yl
59	F	F	H	H	2	H	H	Cyclopropyl
60	F	F	H	H	2	H	H	Ethyl

61	F	F	H	H	2	H	H	iso-Propyl
62	F	F	H	H	2	H	H	$CH_2(2\text{-}Cl\text{-}C_6H_4)$
63	H	H	H	H	2	H	H	$2,4\text{-}F_2\text{-}C_6H_3$
64	H	F	H	H	2	H	H	$2,4\text{-}F_2\text{-}C_6H_3$
65	F	H	F	H	2	H	H	$2,4\text{-}F_2\text{-}C_6H_3$
66	F	H	H	F	2	H	H	$2,4\text{-}F_2\text{-}C_6H_3$
67	H	H	CH_3	F	2	H	H	$2,4\text{-}F_2\text{-}C_6H_3$
68	F	OCH_3	H	H	2	H	H	$2,4\text{-}F_2\text{-}C_6H_3$
69	F	Cl	H	H	2	H	H	$2,4\text{-}F_2\text{-}C_6H_3$
70	Cl	Cl	H	H	2	H	H	$2,4\text{-}F_2\text{-}C_6H_3$

TABLE II

Table II comprises 70 compounds of formula (Ib'):

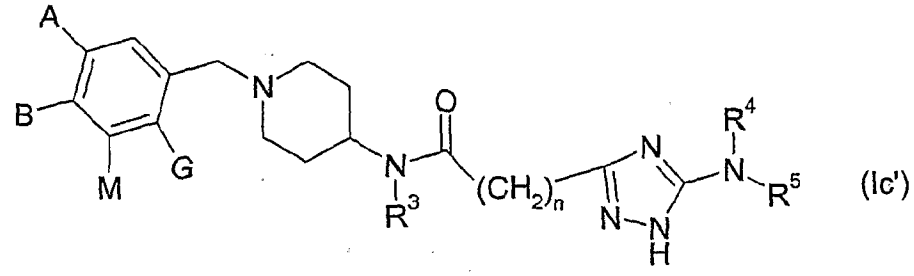


(Ib')

wherein the groups A, B, R^3, n, R^4 and R^5 have the meanings for the correspondingly numbered compound in Table I.

TABLE III

Table III comprises 70 compounds of formula (Ic'):

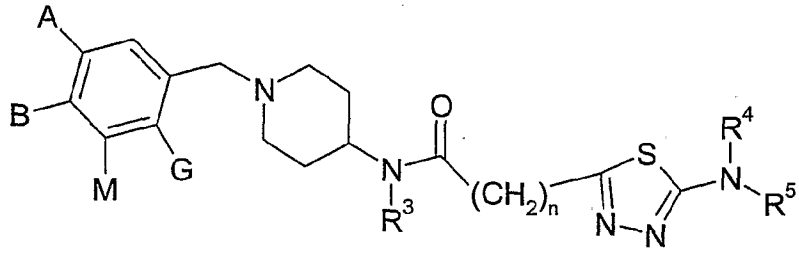


(Ic')

wherein the groups A, B, R^3, n, R^4 and R^5 have the meanings for the correspondingly numbered compound in Table I.

TABLE IV

Table IV comprises 70 compounds of formula (Id'):

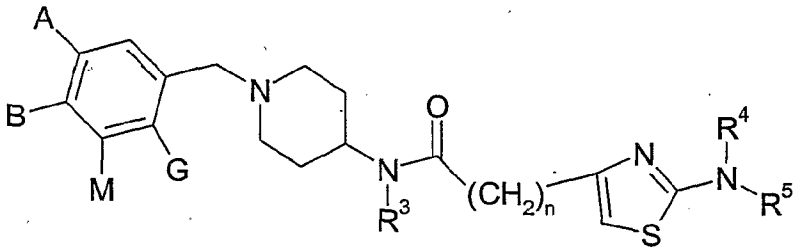


(Id')

wherein the groups A, B, R^3, n, R^4 and R^5 have the meanings for the correspondingly numbered compound in Table I.

TABLE V

Table V comprises 70 compounds of formula (Ie'):

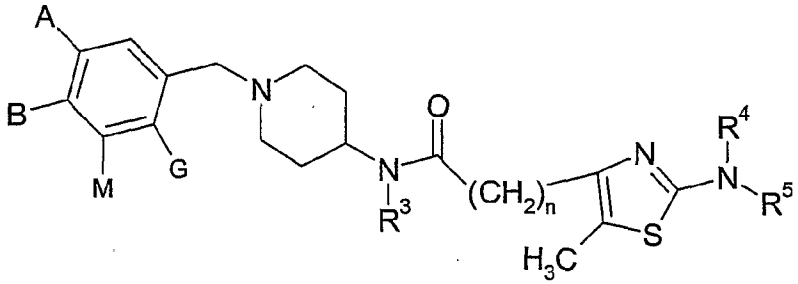


(Ie')

wherein the groups A, B, R^3, n, R^4 and R^5 have the meanings for the correspondingly numbered compound in Table I.

TABLE VI

Table VI comprises 70 compounds of formula (If'):



(If')

wherein the groups A, B, R^3, n, R^4 and R^5 have the meanings for the correspondingly numbered compound in Table I.

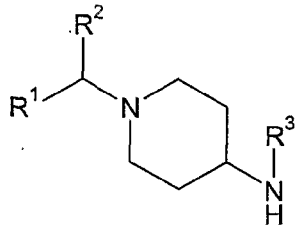
The compounds of the present invention can be prepared by adaptation of the Examples, by adaptation of methods described in the literature or by one of the methods presented below.

Thus, for example, a compound of formula (I) wherein: Y is oxadiazolyl can be prepared as shown in Schemes 1 and 3 below; Y is 1,2,4-triazolyl can be prepared as shown in Scheme 2 below; Y is oxazole or thiazole can be prepared as shown in Schemes 4 (where Z is oxygen or sulphur), 5, 6, 7 or 11; Y is isoxazole can be prepared as shown in Schemes 8, 9 and 10; Y is pyrazole can be prepared as shown in Scheme 10 (or by using hydrazine in place of hyroxylamine, or the chlorohydrazone in place of the chlorooxime in Schemes 8 and 9); Y is 1,3,4-oxadiazole or thiadiazole can be prepared as shown in Scheme 12; Y is isothiazole can be prepared as shown in Schemes 13 and 14; and Y is 1,2,4-thiadiazole can be prepared as shown in Schemes 15 and 16. Compounds wherein Y is imidazole can be prepared by heating an oxazole with ammonia or an amine, for example in ethanol, if necessary under pressure (for example in a bomb).

In the Schemes:

1. R* is hydrogen or alkyl;
2. in Schemes 8 and 9 Z is a suitably protected or masked acid group such that the acid group does not interfere with the intended reaction. For example it can be an ester or amide, or an alkene (which, on ozonolysis, would generate the acid). The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).
3. PyBrOP™ is bromo-tris-pyrrolidino-phosphonium hexafluorophosphate; HATU is O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; HBTU is O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate; EDCI is Ethyl dimethylaminopropyl carbodiimide hydrochloride; HOBT is 1-hydroxybenzotriazole; and, DMAP is dimethylaminopyridine
4. RT is room temperature
5. BuLi is a butyl lithium
6. LDA is lithium diisopropylamide

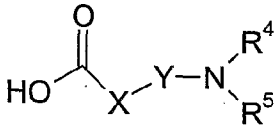
7. A carbodiimide is a coupling agent of the formula –N=C=N-, for example dicyclohexylcarbodiimide or a polymer-bound carbodiimide
8. In Schemes 5, 6, 7, 8, 9, 11, 13, 14 and 15 the final coupling reactions (shown as 'couple') join the final compound with:



can be carried out following literature methods, for example using PyBrOP™ at room temperature and N,N-dimethylformamide (DMF) as solvent.

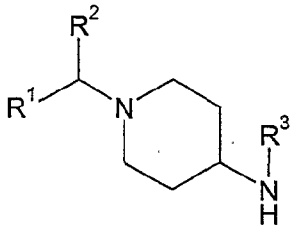
9. Curtius reactions can be carried out under literature conditions, for example diphenylphosphoryl azide / base (for example triethylamine or 1,8-bis dimethylaminonaphthalene), then heat, then water to decompose.

The compounds of the invention can be prepared by coupling a compound of formula (II):



(II)

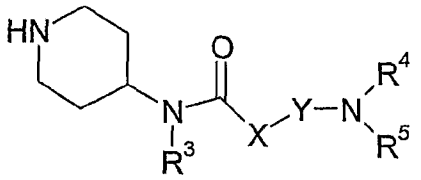
with a compound of formula (III):



(III)

in the presence of a suitable solvent (such as N,N-dimethylformamide) and in the presence of a suitable coupling agent (for example using PyBrOP™; HATU; HBTU; EDCI/HOBT/DMAP) at a temperature in the range 0-50°C.

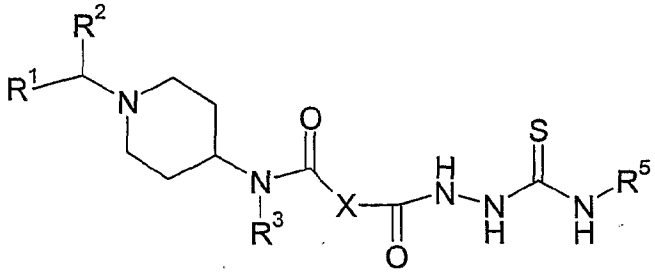
A compound of formula (I) wherein R^2 is hydrogen can be prepared by reacting a compound of formula (IV):



(IV)

with an aldehyde of formula R^1CHO in a suitable solvent (such as N-methylpyrrolidinone) and in the presence of a suitable acid (such as acetic acid); and reducing the product so formed (with, for example, sodium triacetoxyborohydride).

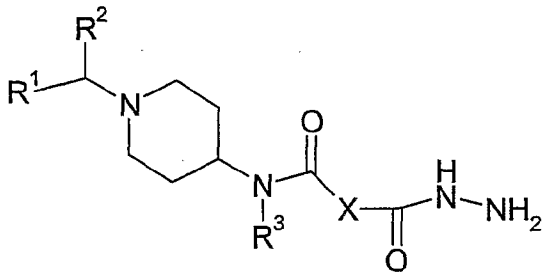
A compound of formula (I) wherein Y is 1,3,4-oxadiazolyl and R^4 is hydrogen can be prepared by heating a compound of formula (V):



(V)

at a suitable temperature (such as in the range 50-100°C) in a suitable solvent (such as dimethylformamide and in the presence of a suitable ring-closure chemical (such as N-cyclohexylcarbodiimide, for example supported on a suitable polymer such as polystyrene).

A compound of formula (V) can be prepared by reacting a compound of formula (VI):



(VI)

with an isothiocyanate of formula R^5NCS, in a suitable solvent (such as dimethylformamide) at a temperature in the range 10-40°C.

The starting compounds of all the Schemes are either commercially available, known in the literature or can be prepared using known techniques.

When intermediates in the processes of the present invention contain reactive groups then these may, depending upon the reaction conditions, need to be protected by

protecting groups. Thus, the preparation of the compounds of the invention may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

The compounds of the invention and intermediates may be isolated from their reaction mixtures, and if necessary further purified, by using standard techniques.

In further aspects the present invention provides processes for the preparation of compounds of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) and (If').

The compounds of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) and (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, have activity as pharmaceuticals, in particular as modulators of chemokine receptor activity. More particularly, the compounds have utility as modulators of the activity of chemokine receptor CCR3.

A further aspect of the invention involves the use of a compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, in the treatment of conditions or diseases in which modulation of the CCR3 chemokine receptor activity is beneficial.

Thus, the compounds of the invention, or a salt thereof, a solvate thereof or a solvate of a salt thereof, may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS). Examples of these conditions include:

(1) **(the respiratory tract)** obstructive airways diseases including chronic obstructive pulmonary disease (COPD); asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, osteoarthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, pemphigus, bullous pemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, inflammatory bowel disease, irritable bowel syndrome, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura; and

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

Thus, the present invention provides a compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined for use in therapy; for example in the treatment of a chemokine mediated disease state (especially a CCR3 mediated disease state) in a mammal, such as man, such as in the treatment of a respiratory disease state (for example asthma and/or rhinitis).

The compounds of the invention, or a salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined, are especially useful in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including

croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a further aspect, the present invention provides the use of a compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy; for example in the treatment of a chemokine mediated disease state (especially a CCR3 mediated disease state) in a mammal, such as man, such as in the treatment of asthma and/or rhinitis.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The invention also provides a method of treating a CCR3 mediated disease state (such as an inflammatory disease state) in a mammal (such as man) suffering from, or at risk of, said disease state, which comprises administering to the mammal a therapeutically effective amount of a compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

A compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, may be used on its own but will generally be administered in the form of a pharmaceutical composition in which the compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending

on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (for example to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, for example by oral administration in the form of tablets, capsules, syrups, powders, aerosols or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

In a further aspect the present invention provides a pharmaceutical combination comprising a compound of formula (I), (Ia), (Ia'), (Ib), (Ib'), (Ic), (Ic'), (Id), (Id'), (Ie), (Ie'), (If) or (If'), or a salt thereof, a solvate thereof or a solvate of a salt thereof, as hereinbefore described, and a histamine antagonist, a steroid, a leukotriene modulator or an IL-5 receptor antibody.

Histamine antagonists include loratidine, desloratidine, fexofenadine, cetirizine, ebastine, astemizole, norastemizole, epinastine or efletirizine.

Steroids include budesonide, fluticasone, mometasone, rofleponide (such as rofleponide palmitate) or formoterol.

Leukotriene modulators include montelukast (such as in its sodium salt form), pranlukast, ZD4407 or zafirlukast.

The present invention will be further explained by reference to the following illustrative Examples.

EXAMPLE 1

This Example illustrates the preparation of 3-[5-(2-chloro-phenylamino)-[1,3,4]oxadiazol-2-yl]- N-[1-(3,4-dichloro-benzyl)-piperidin-4-yl]-propionamide (Compound No. 6 of Table I).

a) N-[1-(3,4-Dichlorobenzyl)-piperidin-4-yl]-3-hydrazinocarbonyl-propionamide.

A solution of 1-(3,4-dichlorobenzyl)-piperidin-4-ylamine (2.2g; JP 59101483) and triethylamine (1.53ml) in dichloromethane (100ml) stirring at ambient temperature was treated with 3-chlorocarbonyl-propionic acid methyl ester (1.14ml). After stirring for 16 hours, the reaction mixture was washed with brine, the organic layer was dried ($MgSO_4$), and evaporated to leave a white solid. This solid was suspended in ethanol (100ml), treated with hydrazine hydrate (5ml) and the resulting mixture was stirred at reflux for 2 hours and then allowed to cool. Water (30ml) was added to the reaction mixture and the ethanol was evaporated. The aqueous residue was then extracted into dichloromethane (6x 50ml), the combined organics were dried ($MgSO_4$) and evaporated to give the subtitle compound as a white solid. (1.9g)

^{1}H NMR (299.98 MHz, $CDCl_3$) 1.38-1.50 (m, 2H), 1.87-1.91 (d, 2H), 2.04-2.15 (m, 2H), 2.44-2.54 (m, 5H), 2.73-2.77 (bd, 2H), 3.41 (s, 2H), 3.63-3.82 (m, 1H), 3.86 (bs, 2H), 5.68-5.71 (bd, 1H), 7.11-7.15 (d, 1H), 7.35-7.38 (d, 1H), 7.41-7.42 (s, 1H).

b) 3-[5-(2-Chloro-phenylamino)-[1,3,4]oxadiazol-2-yl]- N-[1-(3,4-dichloro- benzyl)-piperidin-4-yl]-propionamide

1-Chloro-2-isothiocyanato-benzene (0.112g) and N-[1-(3,4-dichlorobenzyl)-piperidin-4-yl]-3-hydrazinocarbonyl-propionamide (0.20g) were stirred together in dimethylformamide (2ml) at ambient temperature for 2 hours. AM resin (0.324g, Novabiochem, 2% DVB 1.57 mmol/g) was added and the resulting mixture was stirred at ambient temperature for 16 hours. N-Cyclohexylcarbodiimide N-methyl polystyrene HL (0.638g, Novabiochem, 1.69 mmol/g) was added and the resulting mixture was stirred at 80°C for 24 hours, then allowed to cool. The reaction mixture was then filtered, washing with dimethylformamide (2 x 2ml). The combined filtrates were evaporated and the residue was purified by reverse phase HPLC to give the title compound as a white solid. (0.028g, m.pt. 154-156°C, MS $[M+H]^+$ (APCI+) 508/510).

^{1}H NMR (399.98 MHz, DMSO) 1.20-1.42 (m, 2H), 1.60-1.72 (m, 2H), 2.00 (t, 2H), 2.50-2.60 (m, 2H), 2.62-2.72 (m, 2H), 2.93 (t, 2H), 3.41 (s, 2H), 3.41-3.62 (m, 1H), 7.06-7.14 (m, 1H), 7.22-7.40 (m, 2H), 7.41-7.61 (m, 3H), 7.81-8.00 (m, 2H), 9.68 (s, 1H).

The following compounds were made from N-[1-(3,4-dichlorobenzyl)-piperidin-4-yl]-3-hydrazinocarbonyl-propionamide and the appropriate isothiocyanate following the method of Example 1 step b).

Compound No (Table)	m.pt. (°C)	^{1}H NMR	MS $[M+H]^+$ (APCI+)
7(I)	200-213	(DMSO) 1.21-1.48 (m, 2H), 1.60-1.78 (m, 2H), 2.00 (t, 2H), 2.48-2.55 (m, 2H), 2.62-2.78 (m, 2H), 2.91 (t, 2H), 3.42 (s, 2H), 3.43-3.61 (m, 1H), 3.71 (s, 3H), 6.90 (d, 2H), 7.27-7.30 (m, 1H), 7.43 (d, 2H), 7.50-7.60 (m, 2H), 7.87 (d, 1H), 10.07 (s, 1H)	504/506
8(I)	70-82	(DMSO) 1.21-1.48 (m, 2H), 1.60-1.78 (m, 2H), 2.00 (t, 2H), 2.48-2.55 (m, 2H), 2.62-2.78 (m, 2H), 2.91 (t, 2H), 3.42 (s, 2H), 3.43-3.61 (m, 1H), 3.82 (s, 3H), 6.91-7.04 (m, 3H), 7.28 (dd,1H), 7.52-7.60 (m, 2H), 7.81-7.95 (m, 2H), 9.33 (s, 1H)	504/506
9(I)	211-213	($CDCl_3$), 1.20-1.60 (m, 4H), 1.87-1.90 (m, 2H), 2.03-2.18 (m, 2H), 2.70-2.80 (m, 2H), 3.08 (t, 2H), 3.40 (s, 2H), 3.78-3.85 (m, 1H), 5.74 (d, 1H), 5.95 (s, 2H), 6.75-6.84 (m, 2H), 7.02-7.18 (m, 3H), 7.35-7.41 (m, 2H)	518/520

10(I)	105-113	($CDCl_3$), 1.20-1.60 (m, 4H), 1.82-1.95 (m, 2H), 2.03-2.18 (m, 2H), 2.31 (s, 3H), 2.65-2.80 (m, 2H), 3.09 (t, 2H), 3.40 (s, 2H), 3.71-3.90 (m, 1H), 5.74 (d, 1H), 7.00 (s, 1H), 7.11-7.18 (m, 3H), 7.25-7.42 (m, 4H)	488/490
11(I)	194-202	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.02 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.22-7.41 (m, 2H), 7.45-7.63 (m, 2H), 7.90 (d, 1H), 8.00 (d, 1H), 8.20 (d, 1H), 8.69 (s, 1H), 10.62 (s, 1H)	476/8
12(I)	118-136	($CDCl_3$), 1.20-1.60 (m, 4H), 1.81-1.98 (m, 2H), 2.12 (t, 2H), 2.60-2.85 (m, 2H), 3.12 (m, 2H), 3.40 (t, 2H), 3.75-3.90 (m, 1H), 5.69 (d, 1H), 7.00-7.61 (m, 8H)	508/510
38(I)	247-248	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.02 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.18 (s, 3H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.27 (d, 1H), 7.50-7.60 (m, 2H), 7.72 (d, 2H), 7.82-7.93 (m, 3H), 10.97 (s,1H)	552/4
39(I)	214-215	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.02 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.18 (s, 3H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.20-7.30 (m, 1H),7.43-7.70 (m, 4H), 7.75-7.90 (m, 2H), 8.17 (s, 1H), 10.81 (s,1H)	552/4

EXAMPLE 2

The present Example illustrates the preparation of 3-[5-(2-chloro-phenylamino)-[1,3,4]oxadiazol-2-yl]- N-[1-(3,4-difluorobenzyl)-piperidin-4-yl]-propionamide (Compound No. 22 of Table I).

a) N-[1-(3,4-Difluorobenzyl)-piperidin-4-yl]-3-hydrazinocarbonyl-propionamide

A solution of 1-(3,4-difluorobenzyl)-piperidin-4-ylamine (8.7g; EP-A2-0625507) and triethylamine (7.0 ml) in dichloromethane (200ml) stirring at ambient temperature was treated with 3-chlorocarbonyl-propionic acid methyl ester (5.2ml). After stirring for 16 hours, the reaction mixture was washed with brine, the organic layer was dried ($MgSO_4$), and evaporated to leave a white solid. This solid was suspended in ethanol (200ml), treated with hydrazine hydrate (5ml) and the resulting mixture was stirred at reflux for 16 hours and then allowed to cool. Water (30ml) was added to the reaction mixture and the ethanol was evaporated. The aqueous residue was then extracted into dichloromethane (6x 50ml), the combined organics were dried ($MgSO_4$) and evaporated to give the subtitle compound as a white solid. (4.8g)

^{1}H NMR (399.98 MHz, DMSO) 1.31-1.45 (m, 2H), 1.70 (d, 2H), 2.00 (t, 2H), 2.19-2.37 (m, 4H), 2.72 (d, 2H), 3.42 (s, 2H), 3.43-3.59 (m, 1H), 4.15 (s, 2H), 7.02-7.15 (m, 1H), 7.22-7.41 (m, 2H), 7.76 (d, 1H), 8.94 (s, 1H).

b) 3-[5-(2-Chloro-phenylamino)-[1,3,4]oxadiazol-2-yl]- N-[1-(3,4-difluorobenzyl)-piperidin-4-yl]-propionamide

1-Chloro-2-isothiocyanato-benzene (0.125g) and N-[1-(3,4-difluorobenzyl)-piperidin-4-yl]-3-hydrazinocarbonyl-propionamide (0.20g) were stirred together in dimethylformamide (2ml) at ambient temperature for 2 hours. AM resin (0.35g, Novabiochem, 2% DVB 1.57 mmol/g) was added and the resulting mixture was stirred at ambient temperature for 16 hours. N-cyclohexylcarbodiimide N-methyl polystyrene HL (0.682g, Novabiochem, 1.69 mmol/g) was added and the resulting mixture was stirred at 80°C for 24 hours, then allowed to cool. The reaction mixture was then filtered, washing with dimethylformamide (2 x 2ml). The combined filtrates were evaporated and the residue was purified by reverse phase HPLC to give the title compound as a white solid. (0.094g, m.pt. 162-163°C, MS $[M+H]^+$ (APCI+) 476/8).

^{1}H NMR (399.98 MHz, DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.05-7.15 (m, 2H), 7.21-7.42 (m, 3H), 7.45 (d, 1H), 7.94 (d, 1H), 7.96 (d, 1H), 9.69 (s, 1H).

The following compounds were made from N-[1-(3,4-difluorobenzyl)-piperidin-4-yl]-3-hydrazinocarbonyl-propionamide and the appropriate isothiocyanate following the method of Example 2 step b).

Compound No (Table)	m.pt. (°C)	^{1}H NMR	MS $[M+H]^+$ (APCI+)
13(I)	180-181	(DMSO) 1.20-1.50 (m, 2H), 1.78-1.95 (m, 2H), 2.00 (t, 2H), 2.41-2.51 (m, 2H), 2.62-2.73 (m, 2H), 2.95 (t, 2H), 3.31 (s, 3H), 3.42 (s, 2H), 3.43-3.59 (m, 1H), 7.05 -7.10 (m, 1H), 7.15-7.30 (m, 2H), 7.48-7.75 (m, 2H), 7.85-8.00 (m, 2H), 8.08 (s, 1H), 10.48 (s, 1H)	484
14(I)	246-247	(DMSO)1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.50-2.55 (m, 2H), 2.64-2.74 (m, 2H), 2.95 (t, 2H), 3.35 (s, 2H), 3.49-3.60 (m, 1H), 7.11-7.14 (m, 1H), 7.29-7.37 (m, 2H), 7.67-7.81 (m, 4H), 7.89 (d, 1H), 11.00 (s, 1H)	467
15(I)	164-165	(DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.50-2.55 (m, 2H), 2.64-2.74 (m, 2H), 2.95 (t, 2H), 3.35 (s, 2H), 3.49-3.60 (m, 1H), 7.02-7.18 (m, 2H), 7.22-7.40 (m, 3H), 7.89 (d, 1H), 7.95-8.20 (m, 1H), 10.11 (s, 1H)	478
16(I)	132-133	(DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.50-2.55 (m, 2H), 2.64-2.74 (m, 2H), 2.95 (t, 2H), 3.32 (s, 2H), 3.49-3.60 (m, 1H), 3.82 (s, 3H), 6.91-7.08 (m, 3H), 7.10-7.18 (m, 1H), 7.22-7.41 (m, 2H), 7.82-7.92 (m, 2H), 9.34 (s, 1H)	472

17(I)	198-199	(DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.50-2.55 (m, 2H), 2.64-2.74 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.50-3.60 (m, 1H), 7.10-7.40 (m, 6H), 7.87 (d, 1H), 9.70 (s, 1H)	478
18(I)	161-162	(DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.50 (s, 3H), 2.51-2.60 (m, 2H), 2.65 -2.80 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.45-3.60 (m, 1H), 6.80-6.89 (m, 1H), 7.04-7.15 (m, 1H), 7.20-7.40 (m,4H), 7.50 (s, 1H), 7.90 (d, 1H), 10.38 (s, 1H)	488
19(I)	188-189	(DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.65 -2.80 (m, 2H), 2.95 (t, 2H), 3.18-3.20 (m, 2H), 3.42 (s, 2H), 3.45-3.60 (m, 1H), 7.05-7.15 (m, 1H), 7.20-7.60 (m, 4H), 7.77 (d, 1H), 7.90 (d, 1H), 8.00 (s, 1H), 10.81 (s, 1H)	467
20(I)	207-208	(DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.20 (s, 3H), 2.51-2.60 (m, 2H) 2.65 -2.80 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.10 (d, 3H), 7.25-7.45 (m, 4H), 7.90 (d, 1H), 10.19 (s, 1H)	456
21(I)	199-200	(DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.05-7.15 (m,1H), 7.22-7.4 (m, 4H), 7.57 (dd, 2H), 7.90 (d, 1H), 10.51 (s, 1H)	476/8

23(I)	160-161	(DMSO) 1.32-1.42 (m, 2H), 1.67-1.74 (m, 2H), 2.00 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.00-7.40 (m, 6H), 7.88 (d, 1H), 8.00 (t, 1H), 10.13 (s, 1H)	460
24(I)	187-189	(DMSO) 1.32-1.42 (m, 2H), 1.62-1.75 (m, 2H), 2.00 (t, 2H), 2.25 (s, 3H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.00 (t, 1H), 7.08-7.20 (m, 3H), 7.24-7.40 (m, 2H), 7.70 (d, 1H), 7.89 (d, 1H), 9.29 (s, 1H)	456
26(I)	199-200	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.02 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.10-7.15 (m, 1H), 7.22-7.40 (m, 3H), 7.90 (d, 1H), 8.01 (dd, 1H), 8.21 (d, 1H), 8.69 (d, 1H), 10.62 (s, 1H)	443
27(I)	165-166	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.00 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.00 (d, 1H), 7.04-7.15 (m,1H), 7.20-7.45 (m, 4H), 7.69-7.71 (m, 1H), 7.88 (d, 1H), 10.60 (s, 1H)	476/8
28(I)	154-155	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.00 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.09-7.18 (m, 1H), 7.22-7.45 (m, 3H), 7.63-7.64 (m, 1H), 7.90 (d, 1H), 8.00 (d, 1H), 9.89 (s, 1H)	510/2

29(I)	216-217	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.00 (t, 2H), 2.50 -2.59 (m, 2H), 2.62-2.75 (m, 2H), 2.82 (s, 6H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 6.72-6.74 (m, 2H), 7.10-7.15 (m, 1H), 7.25-7.40 (m, 4H), 7.88 (d, 1H), 9.85 (s, 1H)	485
30(I)	213-214	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.00 (t, 2H), 2.45 (s, 3H), 2.50 -2.59 (m, 2H), 2.62-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.10-7.15 (m, 1H), 7.20-7.40 (m, 4H), 7.49 (d, 2H), 7.90 (d, 1H), 10.35 (s, 1H)	488
31(I)	202-204	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.00 (t, 2H), 2.50 -2.59 (m, 2H), 2.62-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 5.97 (s, 2H), 6.85-6.98 (m, 2H), 7.15-7.18 (m, 1H), 7.21-7.22 (m, 1H), 7.23-7.41 (m, 2H), 7.89 (d, 1H), 10.18 (s, 1H)	486
33(I)	236-237	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 1.95-2.05 (m, 5H), 2.50 -2.59 (m, 2H), 2.62-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.08-7.15 (m, 1H), 7.22-7.58 (m, 6H), 7.9 (d, 1H), 9.84 (s, 1H), 10.21 (s, 1H)	499
34(I)	215-216	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 1.95-2.05 (m, 5H), 2.50 -2.59 (m, 2H), 2.62-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.09-7.40 (m, 6H), 7.8 (s, 1H), 7.90 (d, 1H), 9.96 (s, 1H), 10.30 (s, 1H)	499

35(I)	139-140	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 1.95-2.05 (m, 2H), 2.50 -2.59 (m, 2H), 2.62-3.00 (m, 10H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.00 (d, 1H), 7.09-7.45 (m, 4H), 7.50-7.62 (m, 2H), 7.95 (m, 1H), 10.52 (s, 1H)	513
36(I)	183-184	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 1.95-2.05 (m, 2H), 2.50 -2.59 (m, 2H), 2.62-3.00 (m, 10H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 7.10-7.18 (m, 1H), 7.30-7.45 (m, 4H), 7.60 (d, 2H), 7.90 (d, 1H), 10.58 (s, 1H)	513
37(I)	225-226	(DMSO) 1.32-1.45 (m, 2H), 1.62-1.78 (m, 2H), 2.02 (t, 2H), 2.50 -2.59 (m, 2H), 2.65-2.75 (m, 2H), 2.95 (t, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 6.87 (t,1H), 7.10-7.15 (m, 1H), 7.25-7.41 (m, 3H), 7.65 (t, 1H), 7.79 (d, 1H), 7.90 (d, 1H), 8.20 (d, 1H)	443
56(I)		(DMSO) 1.41-1.11(m, 6H), 1.57-1.54(m, 1H), 1.70-1.67(m, 4H), 1.90-1.87(m, 2H) 2.02-1.97(m, 2H), 2.45-2.42(m, 2H), 2.72-2.67(m, 2H), 2.83-2.80(m, 2H), 3.27(m, 2H), 3.43(s, 2H), 3.51-3.50(m, 1H), 7.14-7.13(m, 1H), 7.40-7.26(m, 3H), 7.85-7.83(m, 1H)	448
57(I)		(DMSO) 1.41-1.29(m, 2H) 1.70-1.66(m, 2H), 2.03-1.96(m, 2H), 2.16(s, 6H), 2.48-2.43(m, 2H under DMSO), 2.73-2.69(m, 2H), 2.89-2.84(m, 2H), 3.43(s, 2H), 3.54-3.50(m, 1H), 7.15-7.09(m, 4H), 7.41-7.28(m, 2H), 7.86-7.83(d, 1H), 9.05(s, 1H)	470

58(I)		(DMSO) 1.14-1.04(m, 3H) 1.46-1.24(m, 6H), 1.71-1.60(m, 3H), 2.03-1.96(m, 2H), 2.27-2.20(m, 3H), 2.46-2.44(m, 2H under DMSO), 2.76-2.69(m, 2H), 2.84-2.79(m, 2H), 3.43(s, 2H), 3.52-3.47(m, 1H), 7.15-7.11(m, 1H), 7.41-7.25(m, 3H), 7.85-7.83(d, 1H)	460
59(I)		(DMSO) 0.48-0.43(m, 2H), 0.68-0.63(m, 2H), 1.43-1.31(m, 2H), 1.71-1.67(m, 2H), 2.03-1.96(m, 2H), 1.43-1.31(m, 2H), 1.71-1.67(m, 2H), 2.03-1.96(m, 2H), 2.73-2.69(m, 1H), 2.85-2.80(m, 1H), 3.50(s, 1H), 3.54-3.53(m, 1H), 7.15-7.14(m, 1H), 7.41-7.29(m, 2H), 7.66-7.65(m, 1H), 7.86-7.84(m, 1H)	406
60(I)		(DMSO) 1.14-1.09(t, 3H), 1.43-1.30(m, 2H), 1.71-1.67(m, 2H), 2.03-1.96(m, 2H) 2.46-2.41(m, 2H), 2.73-2.69(m, 2H), 2.4-2.79(m, 2H), 3.19-3.10(m 2H), 3.43 (s, 2H), 3.53-3.49(m, 1H), 7.15-7.10(m, 1H), 7.41-7.28(m, 3H), 7.86-7.83(m, 1H)	394
61(I)		(DMSO) 1.15-1.13(d, 6H), 1.42-1.24(m, 2H), 1.71-1.68(m, 2H), 2.03-1.96(m, 2H), 2.46-2.41(m, 2H), 2.73-2.69(m, 2H), 2.84-2.79(m, 2H), 3.43(s, 2H), 3.63-3.49(m, 2H), 7.15-7.11 (m, 1H), 7.41-7.22(m, 3H), 7.86-7.83(m, 1H)	408
62(I)		(DMSO) 1.61-1.52(m, 2H), 1.95-1.86(m, 2H), 2.57-2.44(m, 2H, under DMSO), 2.90-2.83(m, 2H), 3.12-2.97(m, 2H), 3.37-3.35(m, 2H), 3.77-3.73(m, 1H), 4.28-4.27(m, 2H), 4.44-4.41(m, 2H), 7.36-7.11(m, 3H), 7.47-7.41(m, 2H) 7.65-7.54(m, 2H), 8.08-7.99(m, 2H)	490

EXAMPLE 3

This Example illustrates the preparation of N-[1-(3,4-Dichlorobenzyl)-piperidin-4-yl]-2-(5-phenylamino-[1,3,4]oxadiazol-2-yl)-acetamide (Compound No. 1 of Table I).

a) N-[1-(3,4-Dichlorobenzyl)-piperidin-4-yl]-2-hydrazinocarbonyl-acetamide

A solution of 1-(3,4-dichlorobenzyl)-piperidin-4-ylamine (2.5g) and triethylamine (1.50ml) in dichloromethane (100ml) stirring at ambient temperature was treated with ethylmalonyl chloride (1.35ml). After stirring for 16 hours, the reaction mixture was washed with brine, the organic layer was dried ($MgSO_4$), and evaporated to leave a white solid. This solid was suspended in ethanol (100ml), treated with hydrazine hydrate (5ml) and the resulting mixture was stirred at reflux for 16 hours and then allowed to cool. Water (100ml) was added to the reaction mixture and the ethanol was evaporated. The residue was then extracted with dichloromethane (3 x 100ml), the combined organics were dried ($MgSO_4$), evaporated. The resultant solid was triturated with diethyl ether to give the subtitle compound as a white solid. (2.27g)

^1H NMR (299.98 MHz, $CDCl_3$) 1.44-1.56 (m, 2H), 1.88-1.92 (d, 2H), 2.10-2.17 (t, 2H), 2.74-2.77 (d, 2H), 3.14 (s, 2H), 3.43 (s, 2H), 3.79-3.81 (m, 1H), 3.91 (bs, 2H), 6.62-6.65 (bd, 1H), 7.13-7.15 (m,1H), 7.36-7.39 (m, 1H), 7.42 (s, 1H), 7.82 (bs, 1H).

b) N-[1-(3,4-Dichlorobenzyl)-piperidin-4-yl]-2-(5-phenylamino-[1,3,4]oxadiazol-2-yl)-acetamide

Isothiocyanato-benzene (0.1ml) and N-[1-(3,4-dichlorobenzyl)-piperidin-4-yl]-2-hydrazinocarbonyl-acetamide (0.10g) were stirred together in dimethylformamide (2ml) at ambient temperature for 2 hours. AM resin (0.162g, Novabiochem, 2% DVB 1.57 mmol/g) was added and the resulting mixture was stirred at ambient temperature for 16 hours. N-cyclohexylcarbodiimide N-methyl polystyrene HL (0.319g, Novabiochem, 1.69 mmol/g) was added and the resulting mixture was stirred at 80°C for 24 hours, then allowed to cool. The reaction mixture was then filtered, washing with dimethylformamide (2 x 2ml). The combined filtrates were evaporated and the residue was purified by reverse phase HPLC to give the title compound as a white solid. (0.045g, m.pt. 191-217°C, MS $[M+H]^+$ (APCI+) 460/462).

^{1}H NMR (299.98 MHz, DMSO) 1.36-1.52 (m, 2H), 1.63-1.80 (m, 2H), 1.98-2.10 (m, 2H), 2.70-2.79 (m, 2H), 3.42 (s, 2H), 3.42-3.6 (m, 1H), 3.72 (s, 2H), 6.98 (t, 1H), 7.22-7.35 (m, 3H), 7.43-7.60 (m, 4H), 8.22 (d, 1H).

The following compounds were made from N-[1-(3,4-dichlorobenzyl)-piperidin-4-yl]-2-hydrazinocarbonyl-acetamide and the appropriate isothiocyanate following the method of Example 3 step b).

Compound No (Table)	m.pt. (°C)	^{1}H NMR	MS $[M+H]^+$ (APCI+)
2(I)	199-205	(DMSO) 1.37-1.45 (m, 2H), 1.72-1.79 (m, 2H), 2.00-2.10 (m, 2H), 2.70-2.79 (m, 2H), 3.32 (s, 2H), 3.52-3.6 (m, 1H), 3.69 (s, 2H), 3.71 (s, 3H), 6.91 (d, 2H), 7.28 (d, 1H), 7.43 (d, 2H), 7.53 (s, 1H), 7.58 (d, 1H), 8.20 (d, 1H)	490/492
3(I)	111-118	(CDCl3) 1.4 -2.2 (m, 7H), 2.32 (s, 3H), 2.74-2.80 (m, 2H), 3.42 (s, 2H), 3.75 (s, 2H), 3.79-3.92 (m, 1H), 6.93 (d, 1H), 7.04 (t, 1H), 7.1-7.18 (dd, 1H), 7.20 (d, 1H), 7.22-7.3 (m, 1H), 7.39 (d, 1H), 7.41 (d, 1H), 7.88 (d, 1H)	474/476
5(I)	196-199	(CDCl3) 1.4-2.0 (m, 3H), 1.85-1.95 (m, 2H), 2.12 (t, 2H), 2.70-2.80 (m, 2H), 3.43 (s, 2H), 3.78 (s, 2H), 3.80-3.90 (m, 1H), 6.84 (d, 1H), 7.02 (t, 1H), 7.13 (dd, 1H), 7.30-7.42 (m,4H), 8.28 (d, 1H)	494/496
4(I)	215-223	(DMSO) 1.32-1.50 (m, 2H), 1.65-1.80 (m, 2H), 2.02 (t, 2H), 2.65-2.75 (m, 2H), 3.42 (s, 2H), 3.43-3.60 (m, 1H), 3.73 (s, 2H), 7.29 (d, 1H), 7.39-7.41 (m, 1H), 7.53 (s, 2H), 7.60 (d, 1H), 8.00 (d, 1H), 8.17-8.28 (m, 2H), 8.69 (s,1H)	461/3

EXAMPLE 4

This Example illustrates the preparation of 2-(2-Anilino-1,3-thiazol-4-yl)-*N*-[1-(3,4-dichlorobenzyl)piperidin-4-yl]acetamide (Compound No. 1 of Table V).

2-(2-Anilino-1,3-thiazol-4-yl)-*N*-[1-(3,4-dichlorobenzyl)piperidin-4-yl]acetamide

1-(3,4-Dichlorobenzyl)-4-piperidinamine (138mg) was dissolved in dry dichloroethane (2.5ml) and cooled to -1°C. Trimethylaluminium solution (0.27ml, 2.0M in hexanes) was added dropwise and the solution was stirred at -1°C for 10 min and then 30 min at ambient temperature. Ethyl (2-anilino-1,3-thiazol-5-yl)acetate (133mg) was added and the solution was heated to reflux for 25h. The reaction was allowed to cool and then ammonium chloride solution (saturated aqueous) was added. The suspension was extracted twice with dichloromethane-methanol and once with dichloromethane. The organic phase was concentrated, then suspended in methanol and filtered. The filtrate was loaded on to an SCX cartridge (International Sorbent Technology Isolute® Flash SCX-2), washed with methanol and then product eluted with 0.7M ammonia in methanol. Reverse phase HPLC (Waters Xterra® Column, eluant 0.5% aqueous ammonia : acetonitrile 75-5 : 25-95) gave the title compound (27mg; m.pt. 191-192°C; MS $[M+H]^+$ (APCI+) 475/477).

^{1}H NMR (399.98 MHz, DMSO) δ 1.43 (qd, 2H), 1.74 (dd, 2H), 2.04 (td, 2H), 2.71 (d, 2H), 3.38 (s, 2H), 3.44 (s, 2H), 3.52 - 3.62 (m, 1H), 6.54 (s, 1H), 6.92 (t, 1H), 7.24 - 7.30 (m, 3H), 7.53 (d, 1H), 7.58 (d, 1H), 7.61 (dd, 2H), 7.95 (d, 1H), 10.11 (s, 1H).

EXAMPLE 5

This Example illustrates the preparation of 2-(2-anilino-5-methyl-1,3-thiazol-4-yl)-*N*-[1-(3,4-dichlorobenzyl)piperidin-4-yl]acetamide (Compound No. 1 of Table VI).

Prepared from 1-(3,4-dichlorobenzyl)-4-piperidinamine (138mg) and methyl (2-anilino-5-methyl-1,3-thiazol-4-yl)acetate (141mg) following the method of Example 4 step (c) followed by recrystallisation from aqueous ethanol to give the title compound (7mg; m.pt. 172.5-174°C; MS $[M+H]^+$ (APCI+) 489/491).

^{1}H NMR (399.98 MHz, DMSO) δ 1.44 (qd, 2H), 1.73 (dd, 2H), 2.04 (td, 2H), 2.21 (s, 3H), 2.71 (d, 2H), 3.29 (s, 2H), 3.44 (s, 2H), 3.51 - 3.61 (m, 1H), 6.89 (t, 1H), 7.25 (d, 2H), 7.29 (dd, 1H), 7.53 (d, 1H), 7.58 (d, 3H), 7.90 (d, 1H), 9.91 (s, 1H).

EXAMPLE 6

This Example illustrates the preparation of *N*-[1-(3,4-difluorobenzyl)piperidin-4-yl]-3-{5-[(2,4-difluorophenyl)amino]-1,3,4-thiadiazol-2-yl}propanamide (Compound No. 49 of Table IV).

1-Chloro-2-isothiocyanato-benzene (0.201g) and N-[1-(3,4-difluorobenzyl)-piperidin-4-yl]-3-hydrazinocarbonyl-propionamide (95µl) were stirred together in dimethylformamide (2ml) at ambient temperature for 35 minutes. AM resin (0.35g, Novabiochem, 2% DVB 1.57 mmol/g) was added and the resulting mixture was stirred at ambient temperature for 135 min. The mixture was filtered and methane sulphonic acid (100µl) was added and the solution was heated to 110°C for 4h. The solvent was evaporated and the residue was partitioned between water and ethyl acetate. The aqueous phase was extracted twice with ethyl acetate; the organic phases were washed with water and then brine, then dried, filtered and evaporated. The residue was loaded on to an SCX cartridge (International Sorbent Technology Isolute® Flash SCX-2), washed with methanol and then product eluted with 0.7M ammonia in methanol. Reverse phase HPLC (Waters Xterra® Column, eluant 0.5% aqueous ammonia : acetonitrile 95-25 : 5-75; then 60-40:40-60) gave the title compound (3mg, MS $[M+H]^+$ (APCI+) 494).

^{1}H NMR (399.978 MHz, $CDCl_3$) δ 1.44 (qd, 3H), 1.87 (d, 2H), 2.09 (td, 3H), 2.69 (t, 3H), 2.71 - 2.81 (m, 5H), 3.28 (t, 2H), 3.41 (s, 3H), 3.73 - 3.84 (m, 1H), 5.76 (d, 1H), 6.86 - 6.93 (m, 2H), 6.96 - 7.01 (m, 2H), 7.03 - 7.09 (m, 2H), 7.10 - 7.18 (m, 2H), 7.95 - 8.05 (m, 1H).

EXAMPLE 7

This Example illustrates the preparation of *N*-(1-benzylpiperidin-4-yl)-3-{5-[(2,4-difluorophenyl)amino]-1,3,4-oxadiazol-2-yl} propanamide (Compound No. 63 of Table I).

Step 1: *N*-[1-benzylpiperidin-4-yl]-4-hydrazino-4-oxobutanamide

A solution of 1-(phenylmethyl)-4-piperidinamine, (30g) and triethylamine (29ml) in dichloromethane (500ml) at room temperature was treated dropwise over 20 minutes with 4-chloro-4-oxo-methylbutanoate. The reaction mixture was stirred overnight at room temperature, washed with water and dried ($MgSO_4$). After evaporation the oily residue was dissolved in ethanol (500ml), treated with hydrazine hydrate (30ml) and heated to reflux overnight. After cooling the ethanol was evaporated, the residue was diluted with water

and extracted into dichloromethane (4 x 200ml), the combined organics were dried ($MgSO_4$) and evaporated to leave the subtitle compound as a white solid (20g).

^{1}H NMR (DMSO-d_6) δ 1.41-1.31(m, 2H), 1.70-1.67(m, 2H), 2.00-1.95(m, 2H), 2.73-2.67 (m, 4H), 2.95-2.89(m, 2H), 3.42(s, 2H), 3.56-3.50(m, 1H), 7.13-7.08(m, 1H), 7.36-7.21(m, 6H), 7.89-7.87(m, 1H), 8.01-7.87(m, 1H), 10.11(s, 1H)

Step 2: *N*-(1-benzylpiperidin-4-yl)-3-{5-[(2,4-difluorophenyl)amino]-1,3,4-oxadiazol-2-yl} propanamide

Prepared from *N*-[1-benzylpiperidin-4-yl]-4-hydrazino-4-oxobutanamide following the method of Example 2 step b.

^{1}H NMR (DMSO-d_6) δ 1.41-1.31(m, 2H), 1.70-1.67(m, 2H), 2.00-1.95(m, 2H), 2.73-2.67(m, 4H), 2.95-2.89(m, 2H), 3.42(s, 2H), 3.56-3.50(m, 1H), 7.13-7.08(m, 1H), 7.36-7.21(m, 6H), 7.89-7.87(m, 1H), 8.01-7.87(m, 1H), 10.11(s, 1H)

MS (APCI +ve) 442, M+H

Step 3: 3-{5-[(2,4-difluorophenyl)amino]-1,3,4-oxadiazol-2-yl}-*N*-piperidin-4-ylpropanamide

N-(1-Benzylpiperidin-4-yl)-3-{5-[(2,4-difluorophenyl)amino]-1,3,4-oxadiazol-2-yl}propanamide (8.14g, 18.4mmol) was dissolved in ethanol and hydrogenated over a Pd/C catalyst at 3 bar until the reaction had gone to completion. The reaction mixture was filtered and the filtrate was evaporated to dryness, leaving an off-white solid which was triturated in ether, filtered and then dried in air to leave the subtitle compound (2.68g, 41%).

^{1}H NMR (CD_3OD) δ 0.16-0.12(m, 2H), 0.89-0.86(m, 4H), 1.55-1.48(m, 2H), 1.95-1.79(m, 4H), 2.32-2.11(m, 7H), 2.73-2.69(m, 1H), 5.83-5.78(m, 1H), 5.92-5.86(m, 1H), 6.80-6.74(m, 1H)

MS (APCI +ve) 352, M+H

Step 4: *N*-(1-benzylpiperidin-4-yl)-3-{5-[(2,4-difluorophenyl)amino]-1,3,4-oxadiazol-2-yl} propanamide

To a stirred solution of 3-{5-[(2,4-difluorophenyl)amino]-1,3,4-oxadiazol-2-yl}-*N*-piperidin-4-ylpropanamide (200mg) in N-methylpyrrolidinone (4ml) was added

benzaldehyde (115µl) and glacial acetic acid (0.04ml). The reaction mixture was then heated at 80°C for 1 hour before being left to cool and sodium triacetoxyborohydride (242mg) added. The mixture was then stirred at room temperature for 8 hours before being evaporated to dryness and the residue separated into basic and non-basic components using SCX chromatography. Basic fractions were combined and evaporated to dryness. The residue was purified by RPHPLC (MeCN with NH_3 buffer). Fractions containing the desired product were combined and evaporated to dryness to give the title compound. (92mg).

^{1}H NMR (DMSO-d_6) δ 1.34-1.27(m, 1H) 1.56-1.43(m, 2H), 1.86-1.77(m, 2H), 2.16-2.08(m, 2H), 2.66-2.62(t, 2H), 2.86-2.81(m, 2H), 3.07-3.03(t, 2H), 3.51(s, 2H), 3.71-6.60(m, 1H), 7.08-6.93(m, 2H), 7.32-7.31(m, 4H), 7.95-7.93(m, 1H)

MS (APCI +ve) 442, M+H

The following compounds were made from 3-{5-[(2,4-difluorophenyl)amino]-1,3,4-oxadiazol-2-yl}-*N*-piperidin-4-ylpropanamide and the appropriate benzaldehyde following the method of Example 7 Step 4.

Compound No (Table)	^{1}H NMR	MS $[M+H]^+$ (APCI+)
64 (I)	DMSO: 1.39-1.31(m, 2H) 1.70-1.67(m, 2H), 2.00-1.95(m, 2H), 2.72-2.66(m, 2H), 2.94-2.91(m, 2H), 3.32-3.29(m, 2H, under DMSO), 3.41(s, 2H), 3.53-3.51(m, 1H), 7.18-7.08(m, 2H), 7.36-7.29 (m, 2H), 7.88-7.86(m, 1H), 8.01-7.95(m, 1H), 10.05 (s, 1H)	460
65 (I)	DMSO: 1.42-1.35(m, 2H) 7.17-1.68(m, 2H), 2.49-2.02(m, 2H), 2.6-2.72(m, 2H), 2.95-2.90(m, 2H), 3.32(m, 2H, under DMSO), 3.49(s, 2H), 3.53(m, 1H), 7.26-7.06(m, 3H), 7.36-7.29(m, 1H), 7.89-7.86(m, 1H), 8.00-7.96(m, 1H)	478

66 (I)	DMSO: 1.43-1.33(m, 2H) 1.72-1.68(m, 2H), 2.06-1.98(m, 2H), 2.73-2.69(m, 2H), 2.95-2.91(m, 2H), 3.32-3.29(m, 2H, under DMSO), 3.47(s, 2H), 3.54-3.51(m, 1H), 7.12-6.99(m, 4H), 7.36-7.29(m, 1H), 7.89-7.87(m, 1H), 8.02-7.94(m, 1H), 10.09(s, 1H)	478
67 (I)	DMSO: 1.40-1.24(m, 2H) 1.70-1.67(m, 2H), 2.06-2.02(m, 2H), 2.21(s, 3H), 2.73-2.69(m, 2H), 2.95-2.90(m, 2H), 3.32-2.95(m, 2H, under DMSO), 3.42(s, 2H), 3.55-3.49(m, 1H), 7.19-7.00(m, 3H), 7.36-7.29(m, 1H), 7.87-7.85(m, 1H), 8.02-7.94(m, 1H), 10.10(s, 1H)	474
68 (I)	DMSO: 1.40-1.29(m, 2H) 2.00-1.93(m, 2H) 2.72-2.69(m, 2H), 2.95-2.90(m, 2H), 3.32-3.29(m, 2H), 3.36(m, 2H), 3.52-3.50(m, 1H), 3.81(s, 3H), 7.14-7.01(m, 4H), 7.37-7.29(m, 1H), 7.88-7.85(m, 1H), 8.02-7.94(m, 1H), 10.10(s, 1H)	490
69 (I)	DMSO: 1.42-1.24(m, 2H) 1.71-1.68(m, 2H), 2.05-1.98(m, 2H), 2.72-2.69(m, 2H), 2.95-2.90(m, 2H), 3.31-3.29(m, 2H, under DMSO), 3.45(s, 2H), 3.54-3.51(m, 1H), 7.18-7.08(m, 1H), 7.37-7.29(m, 1H), 7.55-7.49(m, 1H), 7.89-7.87(m, 1H), 8.02-7.94(m, 1H). 10.10(s, 1H)	494
70 (I)	DMSO: 1.42-1.31(m, 2H) 1.71-1.68(m, 2H), 2.05-1.98(m, 2H), 2.73-2.69(m, 2H), 2.95-2.90(m, 2H), 3.31-3.21(m, 2H, under DMSO), 3.44(s, 2H), 3.54-3.51(m, 1H), 7.13-7.08(m, 1H), 7.37-7.27(m, 2H), 7.59-7.53(m, 2H), 7.89-7.86(m, 1H), 8.02-7.94(m, 1H), 10.10(s, 1H)	511

EXAMPLE 8

Pharmacological Analysis

Calcium flux $[Ca^{2+}]_i$ assay

a) Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ ml^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPR plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5μM fibronectin for two hours) at 100ml/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in dimethylsulphoxide and added to a final concentration of 0.1%(v/v) dimethylsulphoxide. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

b) Human monocytes

Human monocytes were isolated from EDTA anticoagulated peripheral blood as previously described (Cunoosamy & Holbrook, J. Leukocyte Biology, 1998, S2, 13). Cells were resuspended ($5x10^6$ ml^{-1}) in LKS and loaded with 5μM FLUO-3/AM + Pluronic F127 2.2μl/ml (Molecular Probes) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $0.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPR plates (Costar). To each well 100μl of cells were added at a concentration of $0.5x10^6$ ml^{-1}. The plates were centrifuged (200g; 5 mins; room temperature) to allow the cells to adhere. After centrifugation the cells were washed twice with LKS (200μl; room temperature).

A compound of the Examples was pre-dissolved in dimethylsulphoxide and added to a final concentration of 0.1%(v/v) dimethylsulphoxide. Assays were initiated by the

addition of an A_{50} concentration of MIP-1α and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

The compounds of the Examples were found to be antagonists of the eotaxin mediated $[Ca^{2+}]_i$ in human eosinophils and/or antagonists of the MIP-1α mediated $[Ca^{2+}]_i$ in human monocytes.

Human eosinophil chemotaxis

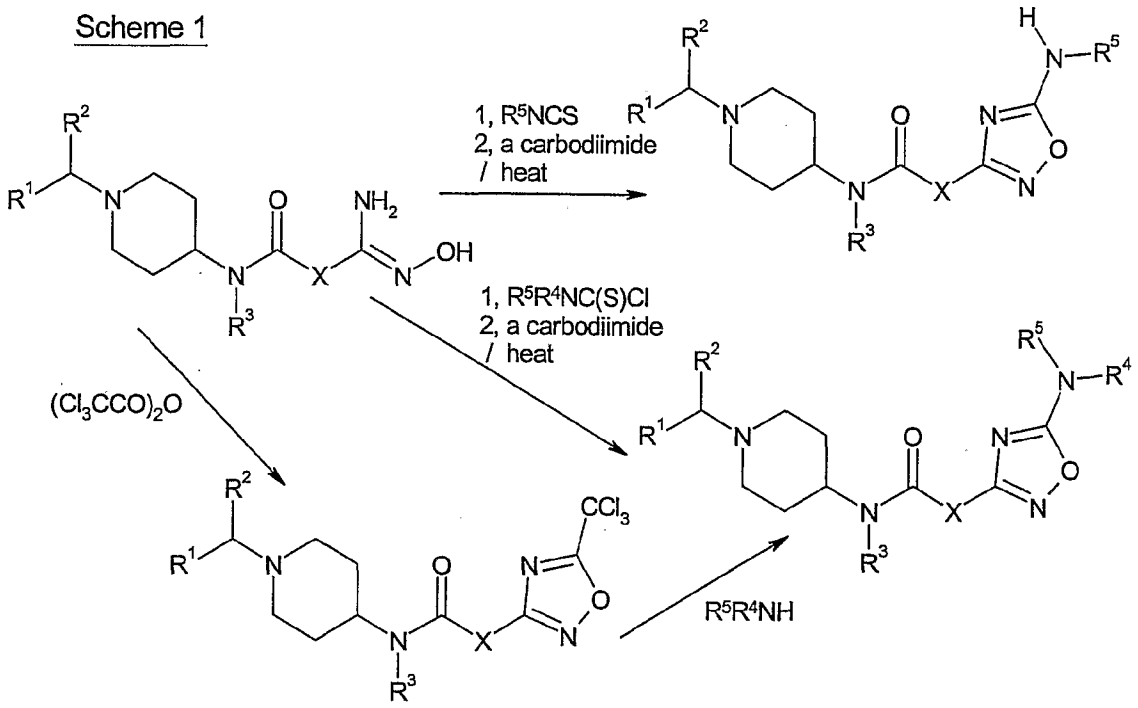
Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ ml^{-1} in RPMI containing 200 IU/ml penicillin, 200 μg/ml streptomycin sulphate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 μl) were pre-incubated for 15 mins at 37° C with 7 μl of either vehicle or compound (100x required final concentration in 10% dimethylsulphoxide). The chemotaxis plate (ChemoTx, 3μm pore, Neuroprobe) was loaded by adding 28μl of a concentration of eotaxin (0.1 to 100nM) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 μl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 μl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Certain compounds of the Examples were found to be antagonists of the eotaxin mediated human eosinophil chemotaxis.

Scheme 1



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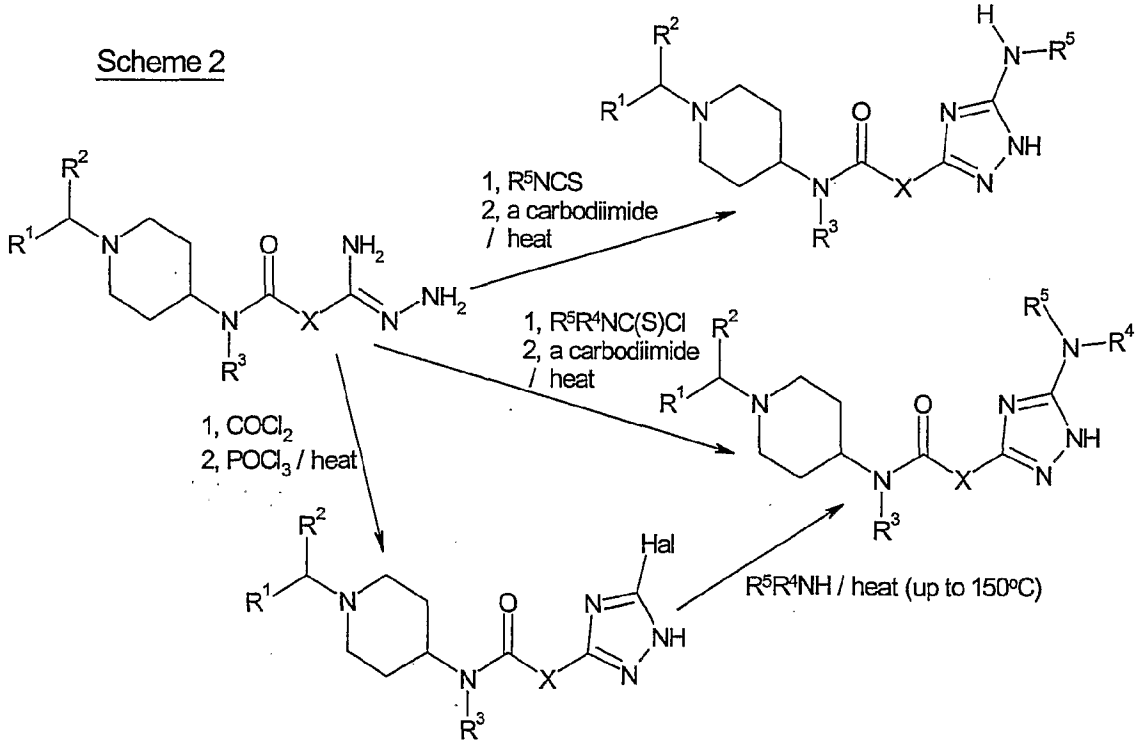
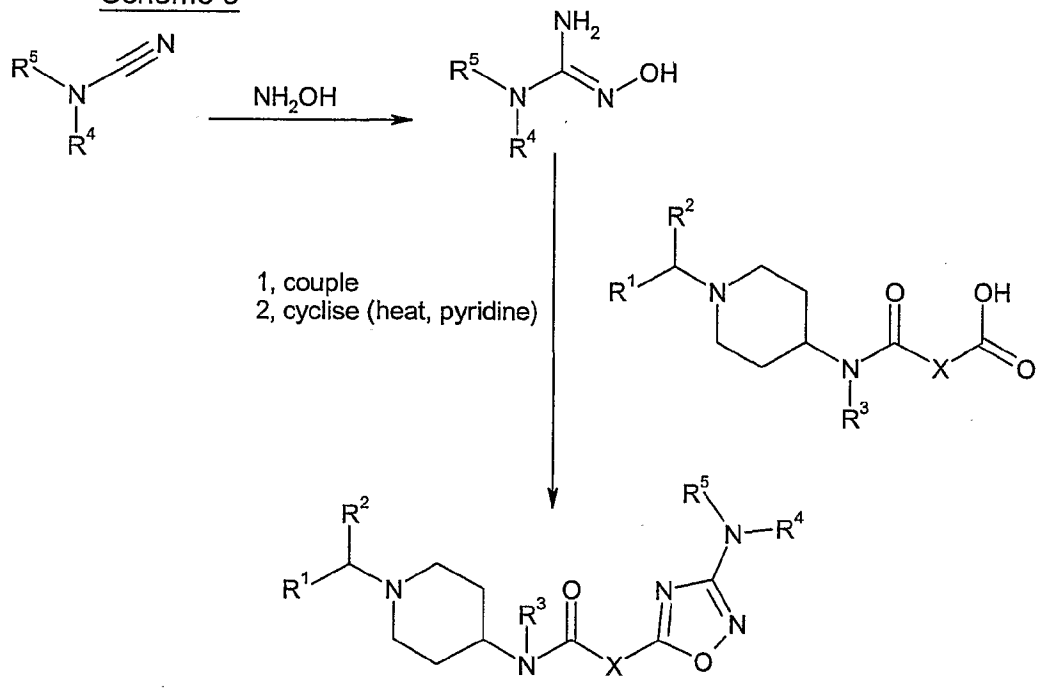
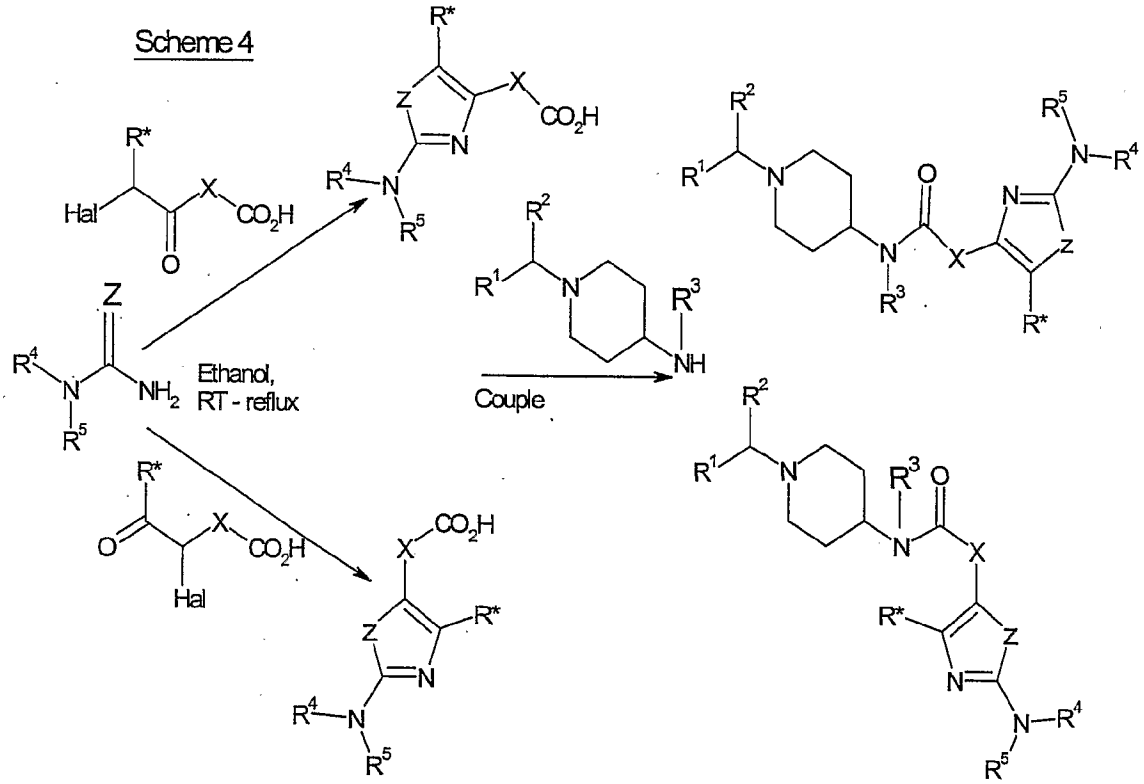


Scheme 3



Scheme 4



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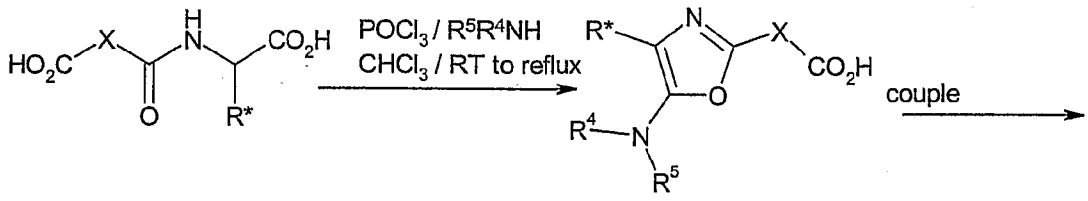
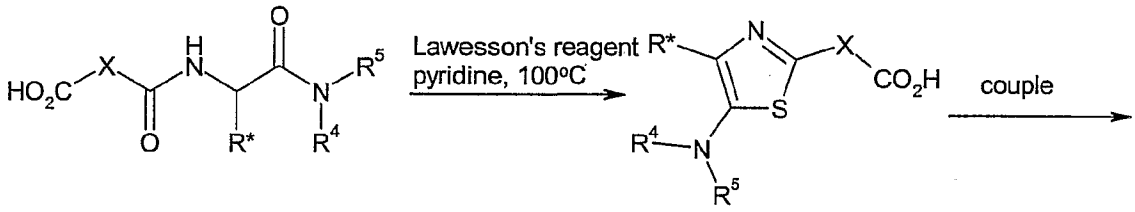
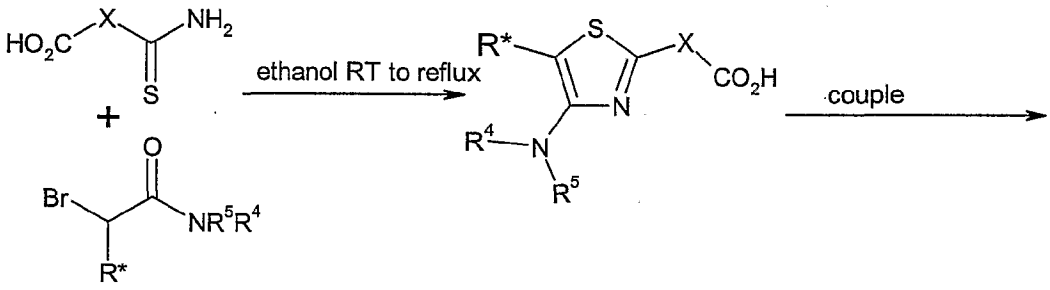


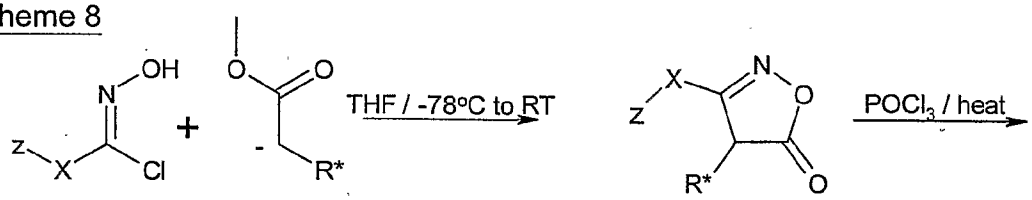
Scheme 6

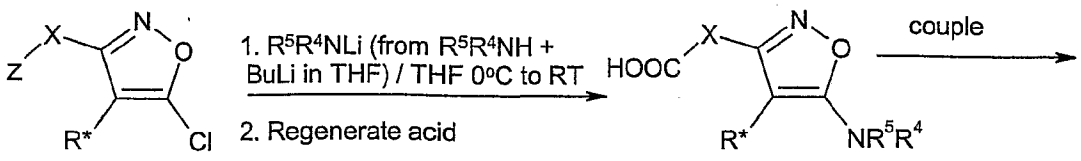


Scheme 7

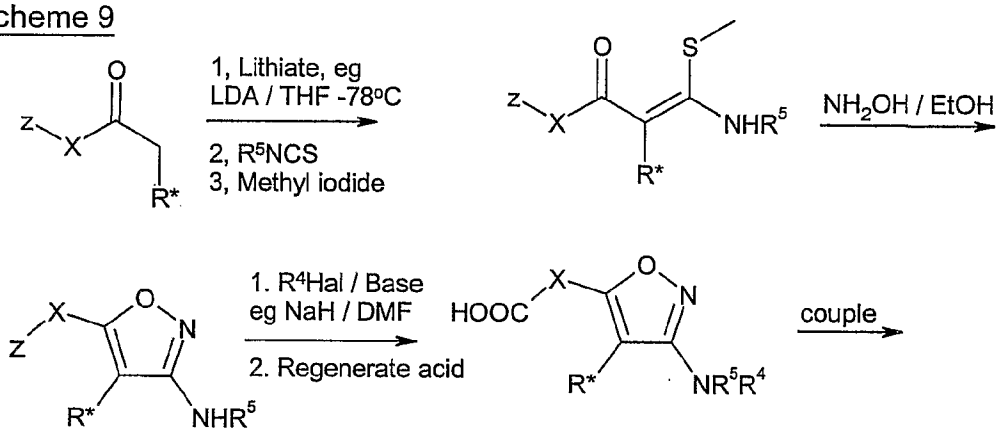


Scheme 8

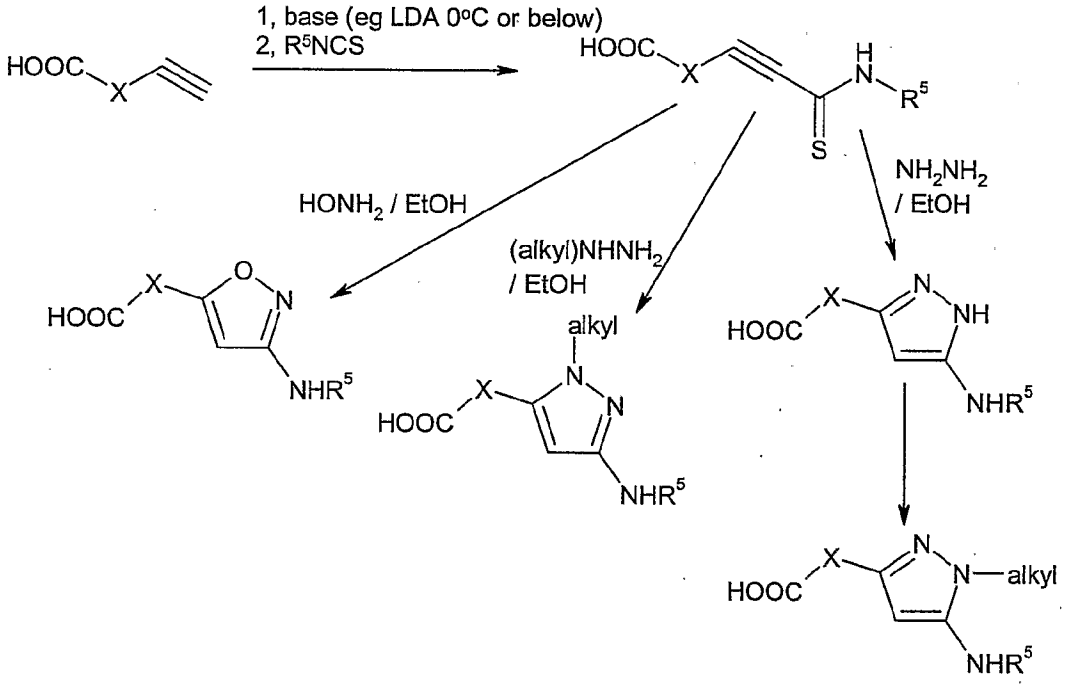




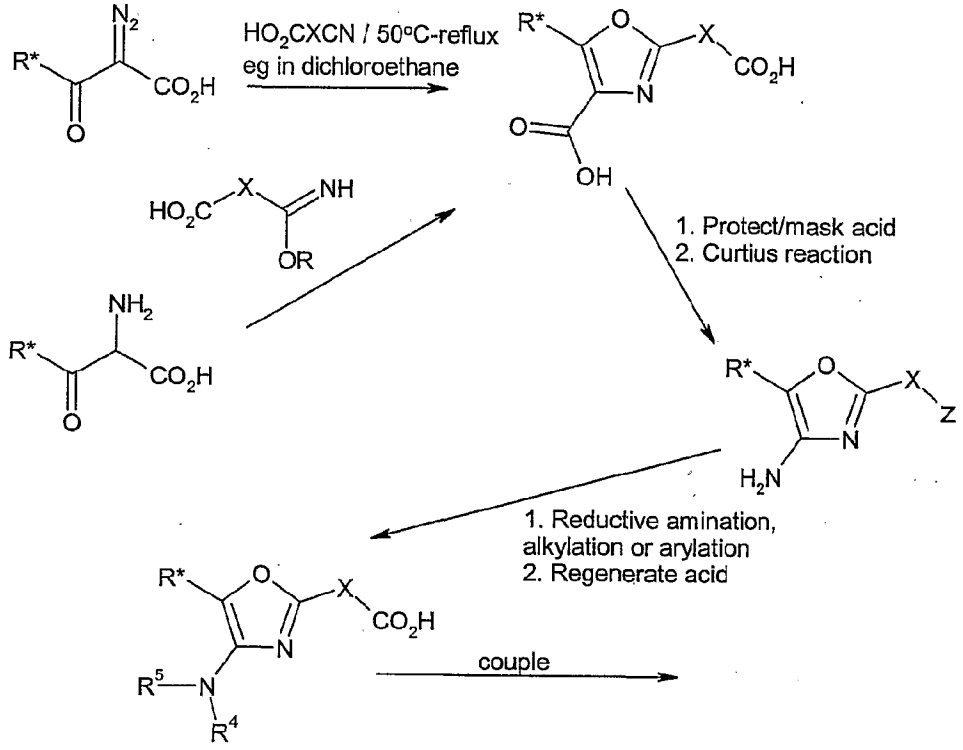
Scheme 9



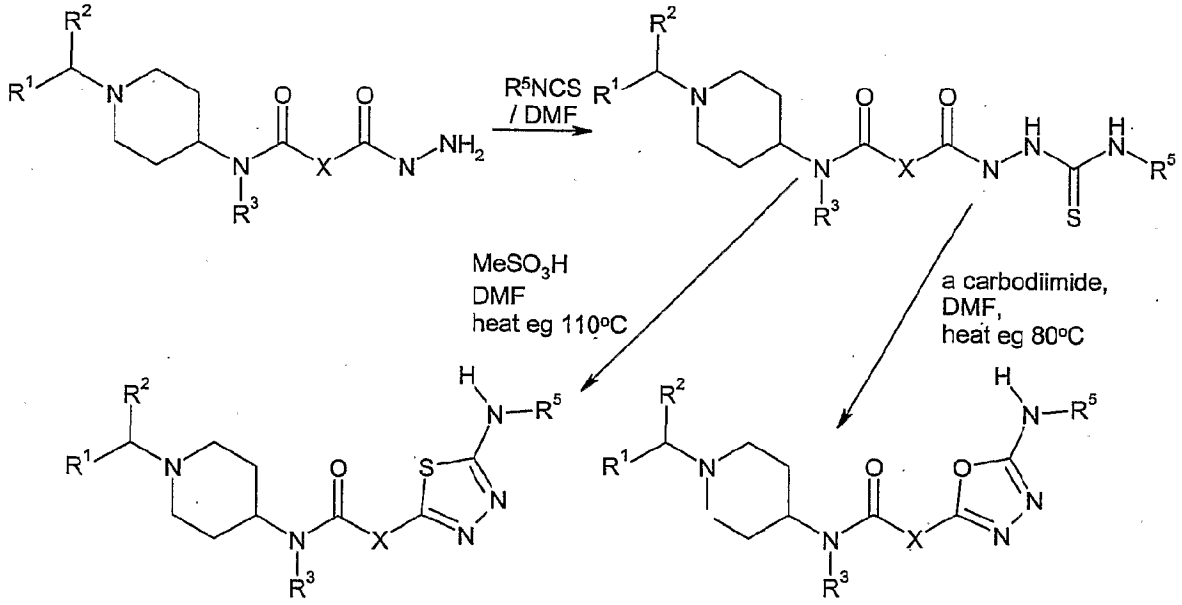
Scheme 10



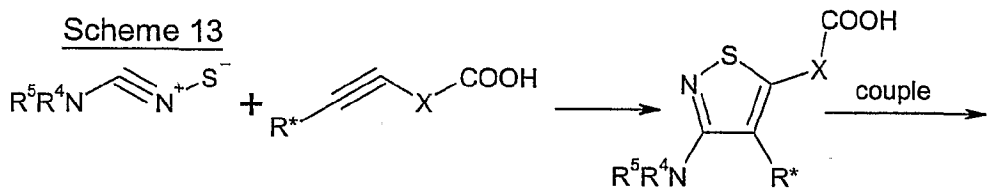
Scheme 11



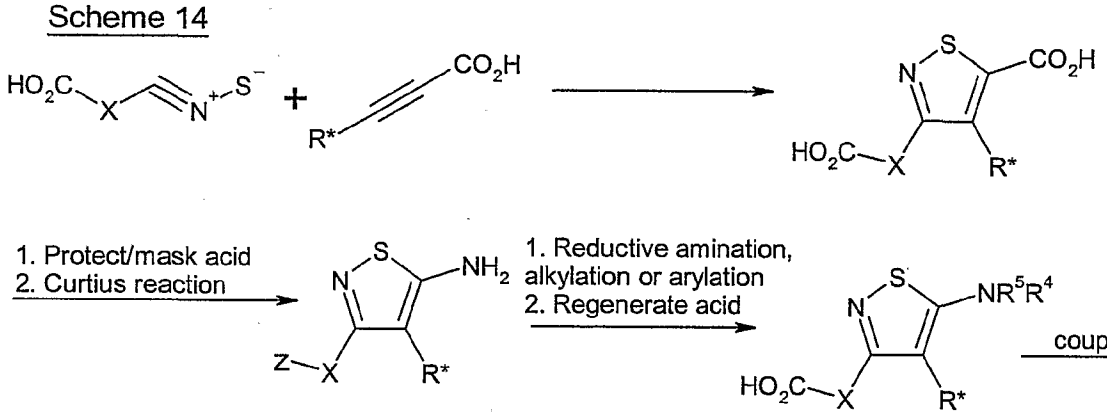
Scheme 12



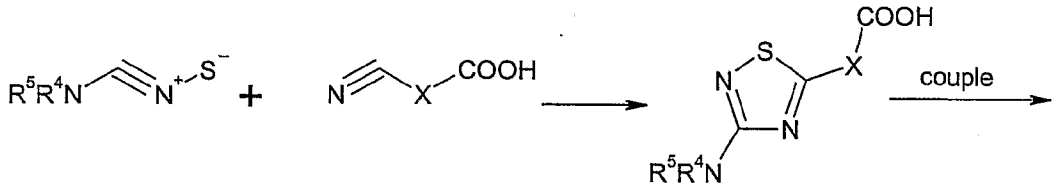
Scheme 13



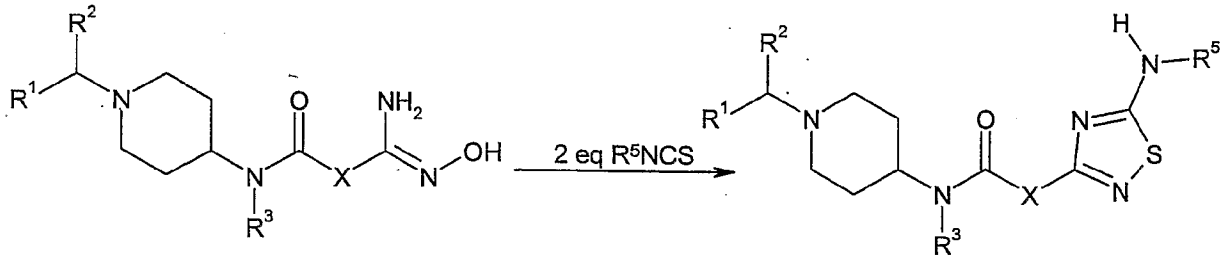
Scheme 14



Scheme 15

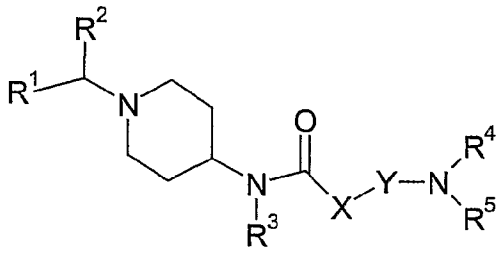


Scheme 16



CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 is phenyl which is optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, nitro or cyano;

R^2, R^3 and R^4 are, independently, hydrogen or C_{1-4} alkyl;

R^5 is C_{1-6} alkyl, aryl, heteroaryl, aryl(C_{1-4})alkyl, heteroaryl(C_{1-4})alkyl or C_{3-8} cycloalkyl; wherein the aryl and heteroaryl moieties of R^5 are optionally substituted by halogen, C_{1-6} alkyl (optionally substituted by halogen, C_{1-6} alkoxy or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)), OR^6, $S(O)_mR^7$, $S(O)_2NR^8R^9$, $NR^{10}S(O)_2R^{11}$, $C(O)R^{12}$, $C(O)NR^{13}R^{14}$, $NR^{15}C(O)R^{16}$, $NR^{17}R^{18}$, $NR^{19}C(O)NR^{20}R^{21}$, methylenedioxy, nitro or cyano;

X is $(CH_2)_n$, where n is 1, 2, 3 or 4;

Y is a 2,4-, 2,5- or 3,5- linking 5-membered heteroaryl ring comprising 2 or 3 heteroatoms independently selected from the group comprising nitrogen, oxygen and sulphur, wherein Y is optionally substituted by C_{1-4} alkyl;

R^6, R^8, R^9, R^{10}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20} and R^{21} are, independently, hydrogen or C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no acetal or aminal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3));

R^7 and R^{11} are, independently, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no thioacetal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3));

R^{12} is hydrogen, C_{1-6} alkyl (optionally substituted by C_{1-6} alkoxy (provided no acetal is formed) or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4}

alkoxy or CF_3)) or C_{1-6} alkoxy (unsubstituted or mono-substituted by C_{1-6} alkoxy or phenyl (itself optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy or CF_3)); or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof.

2. A compound as claimed in claim 1 wherein R^1 is phenyl optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy or halogen.

3. A compound as claimed in claim 1 or 2 wherein R^2, R^3 and R^4 are all hydrogen.

4. A compound as claimed in claim 1, 2 or 3 wherein R^5 is C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, monocyclic heteroaryl, benzyl or monocyclic heteroarylmethyl, wherein the phenyl and heteroaryl moieties of R^5 are optionally substituted by halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, methylenedioxy, $C(O)(C_{1-4}$ alkyl), C_{1-4} thioalkyl, cyano, $N(C_{1-4}$ alkyl$)_2$, $NHC(O)(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$ or $S(O)_2(C_{1-4}$ alkyl).

5. A compound as claimed in claim 1, 2, 3 or 4 wherein X is $(CH_2)_2$.

6. A compound as claimed in claim 1, 2, 3, 4 or 5 wherein Y is 2,5-linked thiazolyl ring (optionally substituted with C_{1-4} alkyl), or a 3,5-linked 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl or 1,3,4-thiadiazolyl ring

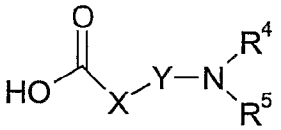
7. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof, as claimed in claim 1, and a pharmaceutically acceptable diluent or carrier therefor.

8. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1 to 6, for use in therapy.

9. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1 to 6, in the manufacture of a medicament for use in therapy.

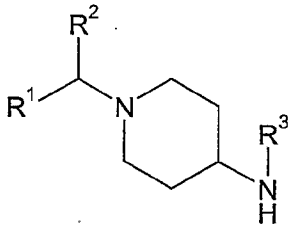
10. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1 to 6.

11. A process for preparing a compound as claimed in claim 1 which comprises:
A. coupling a compound of formula (II):



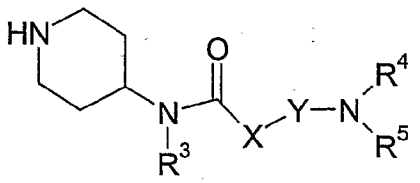
(II)

with a compound of formula (III):



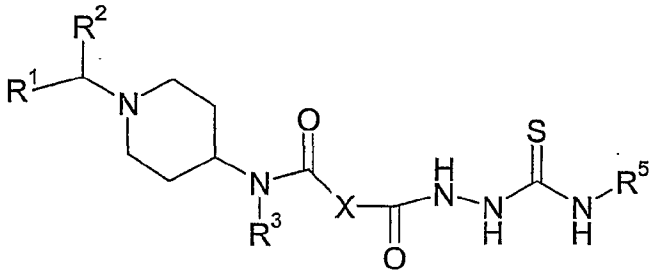
(III)

in a suitable solvent, in the presence of a suitable coupling agent and at a temperature in the range 0-50°C; or,
B. where R^2 is hydrogen, reacting a compound of formula (IV):



(IV)

with an aldehyde of formula R^1CHO in a suitable solvent and in the presence of a suitable acid; and reducing the product so formed; or,
C. where Y is 1,3,4-oxadiazolyl and R^4 is hydrogen, heating a compound of formula (V):



(V)

at a suitable temperature, in a suitable solvent and in the presence of a suitable ring-closure chemical.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00269

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/12, 401/14, 405/12, 405/14, 411/12, 411/14, 413/12, 413/14, 417/12,417/14,419/12, 419/14, A61K 31/4525, 31/4535, 31/4545, A61P 11/00, 17/00, 29/00, 37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO INTERNAL, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0187839 A1 (ASTRAZENECA AB), 22 November 2001 (22.11.01) --	1-11
P,X	WO 0114333 A1 (ASTRAZENECA UK LIMITED), 1 March 2001 (01.03.01) --	1-11
X	WO 9925686 A1 (TEIJIN LIMITED), 27 May 1999 (27.05.99) --	1-11
X	WO 0069820 A1 (COMBICHEM, INC.), 23 November 2000 (23.11.00) --	1-11

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 June 2002	06 -06- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Viveca Norén/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00269

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0053600 A1 (BANYU PHARMACEUTICAL CO. LTD.), 14 Sept 2000 (14.09.00) -- --------	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/05/02

International application No.
PCT/SE 02/00269

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0187839 A1	22/11/01	AU 5898101 A	26/11/01
		GB 0011838 D	00/00/00
WO 0114333 A1	01/03/01	AU 6461600 A	19/03/01
		SE 9902987 D	00/00/00
WO 9925686 A1	27/05/99	AU 744685 B	28/02/02
		AU 1374199 A	07/06/99
		BG 104441 A	31/01/01
		BR 9814645 A	31/07/01
		CA 2309328 A	27/05/99
		CN 1279668 T	10/01/01
		EE 200000294 A	15/08/01
		EP 1030840 A	30/08/00
		HR 20000214 A	31/12/01
		HU 0004200 A	28/03/01
		JP 2001523661 T	27/11/01
		NO 20002486 A	18/07/00
		PL 342207 A	21/05/01
		SK 5532000 A	12/02/01
		TR 200001399 T	00/00/00
WO 0069820 A1	23/11/00	AU 5011300 A	05/12/00
		EP 1181278 A	27/02/02
WO 0053600 A1	14/09/00	AU 2942000 A	28/09/00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00269

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

see next page

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 10 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.